

Proceedings of the British Cardiac Society

THE 1992 ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Harrogate International Conference Centre from 26 to 29 May.

The President, Dr D A Chamberlain, took the Chair during private business. Dr J G F Cleland was elected as Assistant Honorary Secretary, and Dr D Dymond took over as Honorary Secretary from Dr P Oldershaw. Dr R Boyle was elected to Council on the retirement of Prof R W F Campbell.

Deaths during the year:

W T Brandt, J S Fleming, S Oram, L Schamroth, Sir Horace Smirk, M Suzman, R J Vakil, P Yu.

New Members 1992:

R I Bain (Grimsby); R Blackwood (Wexham); N Cary (Cambridge); K Chan (Leicester); M Cheesman (Wesbury on Trym); M Colquhoun (Hereford); G Dalzell (London-derry); J W Dean (London); M de Belder (London); J Dyet (Hull); J Francis (Stafford); R Franklin (Harefield); M Griffith (Newcastle); L Hughes (London); R Jeffrey (Aberdeen); G Kaye (Leeds); D Kitchiner (Liverpool); E Ladusans (Manchester); D Maciver (Birmingham); J M Morgan (London); J Murphy (Darlington); D Northridge (Cardiff); J Poloniecki (London); M Pye (London); A Shah (Cardiff); J Smyllie (Leeds); U Somasundram (Northallerton); J Stewart (London); D Thompson (Leicester); J Weil (Leeds); F Wells (Cambridge); P Whincup (London); U Wijayawardhana (Lincoln); C Wilson (Belfast); C Wren (Newcastle); A Zzulka (Leeds).

New Corresponding Member:

Prof M Sekiguchi (Japan)

The following are abstracts of the papers that were presented.

Clinical and echocardiographic survey of valvar and myocardial disease in a representative sample of elderly people in the general population

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To measure the frequency of valvar and myocardial disease in the elderly (>64) general population, an age and sex stratified random sample of Southampton residents was asked to answer a standard questionnaire and have a physical and echocardiographic examination. Clinical data (28 demographic, 82 symptom, and 96 physical variables for each subject) were collected from 259 people (a response rate of 64%). In 236 (131 men) a full echocardiographic data set (56 variables) was obtained. Symptoms of possible cardiac origin or abnormal physical cardiac findings or both were present in 197 (83% (100 men)), 170 (72% (84 men)), and 111 (47% (51 men)), respectively. The clinical

diagnoses were aortic stenosis in four women (2%), aortic regurgitation in 13 (5.5% (six men)), mitral regurgitation in 13 (5.5% (7 men)), mitral stenosis in one woman (1%), tricuspid regurgitation in five (2% (two men)), congestive cardiac failure in six (2.5% (two men)) and hypertension in 33 (14% (19 men)). Echo and Doppler abnormalities or both, found in 105 (44% (55 men)) of which 10 were unsuspected clinically, were aortic stenosis in six (2.5% (two men)), aortic regurgitation in 35 (14% (15 men)), mitral regurgitation in 16 (6% (seven men)), mitral valve prolapse in two men (1%), tricuspid regurgitation in 15 (6% (five men)), cardiomyopathy in one man (0.5%) and atrial septal defect in seven (3% (five men)). Those with cardiac symptoms and signs were older (mean age 74.1 (range 65-99) v 71.1 (65-87)), of lower social class (87 of 105 in the lowest three classes), and had a high frequency of smoking (37/48), hypertension (74/78), and diabetes (13/14). Overall the positive and negative predictive values (with respect to echo) of cardiac symptoms were 0.43 and 0.54, of cardiac signs 0.51 and 0.73, and of either or both 0.48 and 0.74 respectively.

Thus in the elderly, the prevalence of valvar and myocardial disease may be as high as 44%, 9.5% of which may not be clinically manifest.

Cost-benefit analysis of radiofrequency catheter ablation for cure of supraventricular arrhythmias

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Radiofrequency catheter ablation is becoming established as an effective treatment for physiological cure of supraventricular arrhythmias involving an extra pathway, such as those associated with the Wolff-Parkinson-White syndrome and atrioventricular (AV) nodal re-entrant tachycardia. All new procedures have cost implications, and we have tried to assess these for this new procedure in comparison with medical management or specific arrhythmia surgery. In the last year, specific ablation has been attempted in 53 patients (mean age 30) with extra pathways (47 with accessory AV pathways, six with slow AV nodal pathways) with an overall success rate of 39/53 (74%). Our overall surgical success rate is >95%. Surveying 20 consecutive ablation patients, there were eight emergency inpatient admissions for tachycardia in the year before ablation, with a total of 30 days spent in hospital as a result, and 11 other visits to a casualty department. The annual costs for a medical patient include the cost of drugs (mean 1.25 drugs/patient at any one time), using the cost of flecainide (the drug most frequently taken by the patients) as the index, and two routine outpatient visits with electrocardiograms per year plus the cost of emergency care. Catheter ablation and surgical costs include the cost of the failures. Successfully treated patients were discharged after a single follow up. Surgical costs include the cost of prior electrophysiological study, but this is not included in catheter ablation costs as it is now our practice to combine electrophysiological study with ablation, and costs have been calculated on this basis. In 1991, relative costs of catheter ablation and medical treatment were 4.2:1, and surgery in comparison with catheter ablation was 2.1:1.

Surgical patients returned to work an average of 70 days after operation, whereas catheter ablation patients returned to work within an average of five days.

Catheter ablation offers immediate cost benefits to surgery, and cost benefits in comparison with medical treatment over a five year period. As the average age was only 30, and the patients had otherwise normal life expectancy, ablation offers good cost benefits overall.

Confidential enquiry into cardiac catheter complications

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The confidential enquiry into cardiac catheter complications (CECCC) is a voluntary audit of such complications set up under the joint auspices of the British Cardiac Society and the Royal College of Physicians. Data collection started in August 1990 with a pilot study in five centres. By November 1991 16 centres were participating. The total number of registered patients (on 30 November 1991) was 18 734. Of these, 16 577 had undergone diagnostic cardiac catheterisation and 2165 percutaneous coronary angioplasty. In centres undertaking adult cardiology left heart catheter and coronary angiography accounted for a mean of 85% of all studies, but in one centre the proportion was only 64%. In centres undertaking percutaneous coronary angioplasty the median ratio of coronary angioplasty to coronary angiographic studies was 1:4.5. 220 complications (defined as untoward events that threatened life or prolonged hospital stay) were registered. The complication rate for diagnostic angiography was 0.93% and for coronary angioplasty 3.00% (unsuccessful angioplasty was not, in itself, a complication). Mortality was 0.11% for diagnostic angiography and 0.23% for percutaneous coronary angioplasty. These results (which may represent the results of selected well organised and well motivated centres) compare well with recent data from the United States.

Analysis of individual complications showed noticeably different patterns between centres, which may reflect differences in catheter techniques. Feedback to the centres concerned has been provided. Confidential enquiry into cardiac catheter complications provides a framework for audit, and for continuing research on ways of further reducing catheter morbidity.

Coronary bypass: a district general hospital's perspective

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Freeman Road Hospital, Newcastle upon Tyne

We reviewed the experience in our hospital of surgery for obstructive coronary artery disease for a six year period ending December 1989. During this time a series of 101 consecutive patients from our district general hospital underwent coronary artery bypass grafting at the regional cardiothoracic centre. Our hospital has one cardiologist and seven physicians, all of whom participate in emergency receptions. Patients admitted to the coronary care unit remain the responsibility of the admitting consultant and are seen by the cardiologist on request. The cardiologist has full access to the facilities at the regional cardiothoracic centre. There was a wide variation between individual physicians in the numbers of patients referred for cardiological

evaluation who ultimately underwent coronary artery bypass surgery (range 2 to 11). Patients admitted during physician receptions were about half as likely to receive surgery when compared with patients admitted on the cardiologist's receptions. This was a relatively young series of patients with a mean age of 56 (range 33 to 76) with advanced coronary artery disease; 19% left main coronary artery stenosis and 72% three vessel coronary artery disease in those without left main stem disease. The group had severe symptoms reflected by a 36% incidence of emergency surgery for refractory unstable angina and with patients taking a mean of 2.5 (range 0 to 3) anti-anginal drugs at the time of angiography. Emergency procedures accounted for 46% of operations performed. Operative results were good especially when the severity of disease and the high proportion of emergency operations is considered; there was a 4% operative mortality with 63% of patients well and taking no regular anti-anginal treatment at a mean follow up of five years.

We conclude that surgery provided an effective treatment for this selected group of high risk patients with coronary artery disease. The wide variation between different physicians in the number of patients referred who progressed to bypass grafting and the fact that patients admitted on a physician's reception were less likely to undergo bypass surgery suggests, however, that some patients who would have benefited from surgery may have been denied this form of treatment.

Monitoring cardiac arrest management in an accident and emergency department with a video camera

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Assessment of the resuscitation skills of medical and nursing staff, by questionnaires, manikins, and simulated cardiac arrests, has shown deficiencies that may reduce the chances of successful outcome. Video material is already used as a teaching aid to demonstrate ideal cardiac arrest management. We describe the use of a video camera as part of an audit of true cardiac arrests. The camera is placed in the resuscitation room of the accident and emergency department to provide a fixed field of view, and a microphone is positioned conveniently. The system is activated before the arrival of expected collapse cases brought in by ambulance, to record the preparation of equipment and the management of the resuscitation attempt. Personnel who have taken part in the resuscitation are encouraged to watch the tape recording, informally, with a senior member of staff, before it is wiped clean after a week. A review of the first 10 cases showed deficiencies both of an individual nature (improper rate of chest compressions, improper defibrillator technique), and of a general nature (poor organisation, overcrowding of the resuscitation room, and prolonged interruptions in cardiac massage).

In future it will be possible to develop simultaneous electrocardiographic recording to assess arrhythmia recognition, an automatic switch on device to maximise cases recorded, and multiple cameras to provide views of the whole room. The system will become a useful audit tool leading to improved resuscitation skills.

The effect of cardiac catheterisation facilities on the rate of coronary artery bypass grafting in Scotland

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In Scotland, in 1988, the Scottish Home and Health Department set a target of 350 coronary bypass operations/million/year and achieved a rate of 345 in 1990 (OPCS4 K40-46). There are 12 Health Boards in mainland Scotland. The rate of coronary bypass surgery ranged from 254/million (Dumfries) to 415/million (Greater Glasgow). The mortality from ischaemic heart disease (ICD 410-414) ranged from 318/100 000 (Lothian) to 420/100 000 (Dumfries and Galloway). There was no relation between the death rate from ischaemic heart disease and the rate of coronary bypass surgery. Four Health Boards (all teaching centres) have facilities for cardiac catheterisation and of these three perform coronary bypass surgery. In 1990 the rate of cardiac catheterisation (OPCS4 K63 and K65) ranged from 80/100 000 (Highland) to 171/100 000 (Grampian). There was no relation between death rate from IHD and rate of cardiac catheterisation. Rate of cardiac catheterisation and coronary bypass surgery correlated strongly ($R = 0.8$). The population of the four Health Boards performing cardiac catheterisation was 2,573,715 *v* 2,437,910 in the remaining eight Health Boards; the mortality from ischaemic heart disease was similar—352 *v* 363/100 000. The rate of cardiac catheterisation was 55% higher in those four Health Boards which performed this (144 *v* 93/100 000). The rate of coronary bypass surgery was 43% higher (387 *v* 271/million).

The rate of cardiac catheterisation is a major determinant of the rate of coronary bypass surgery. If those Health Boards which did not achieve the Scottish Home and Health Department target for coronary bypass surgery wish to do so, then this will require them to appoint more cardiologists with facilities for the full investigation of patients with ischaemic heart disease.

Balloon dilatation of the aortic valve for severe symptomatic aortic stenosis in early infancy: the treatment of choice?

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Severe aortic stenosis in the neonatal period has a high mortality, even with prompt surgical treatment. During a 2.5 year period, 10 consecutive infants with severe aortic stenosis have been treated by balloon dilatation of the aortic valve. All patients were symptomatic at <6 weeks of age, eight in the first week. Associated abnormalities included coarctation of the aorta in five patients (severe in three, mild/moderate in two), complete atrioventricular septal defect one patient, severe mitral regurgitation one patient, and endocardial fibroelastosis in seven patients (severe in three). A percutaneous approach via the femoral artery was used with a valvoplasty balloon of diameter equal to or 1 mm less than the aortic annulus diameter measured echocardiographically. Coexisting severe coarctation was treated by balloon dilatation of the aorta in two patients and surgical repair in one patient. Symptomatic improvement with return of peripheral pulses and improvement of heart failure occurred in eight patients (80%). Two patients died despite adequate dilatation shown at post mortem examination. One had severe left

ventricular hypoplasia, the other a very dysplastic valve. Later death occurred in three patients with associated cardiac abnormalities (one atrioventricular septal defect, one mitral regurgitation, one endocardial fibroelastosis + coarctation). Necropsy in two patients showed relief of commissural fusion. Complications included guide wire perforation of the left ventricle in one patient and loss of femoral pulse in four patients. The presence of associated abnormalities and the degree of left ventricular hypoplasia were the main determinants of survival. Only 1/6 patients with a left ventricular diastolic diameter of <2.0 cm survives. The four patients with left ventricular diastolic diameter >2.0 cm are alive and well. The five survivors (50%) have been followed up for two to 24 (mean 13) months. Four are asymptomatic and have mild to moderate residual aortic stenosis; one with severe endocardial fibroelastosis requires diuretic therapy.

Balloon dilatation of the aortic valve offers a promising alternative to surgical valvotomy in infants with severe aortic stenosis. Coarctation frequently coexists and may also be treated by balloon dilatation.

Balloon dilatation for aortic stenosis: age at presentation is an important determinant of the outcome

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Balloon dilatation of the aortic valve was attempted in 38 children over a five year period. The age at presentation was <1 week in nine, <1 month in five, 1 month to 1 year in eight, and >1 year in 16. Of the nine patients presenting <3 days of age, there were no survivors. All presented with severe congestive cardiac failure, required a prostaglandin infusion, and had endocardial fibroelastosis. In three of these, procedural complications contributed to the fatal outcome: arterial damage in two and left ventricular perforation in one. The other six all died between 1 and 185 days after balloon dilatation from left ventricular dysfunction despite technically successful dilatations (augmented by surgical valvotomy in two). A successful outcome was obtained in four of the five patients treated between one and four weeks of age: they now have Doppler gradients between 25 and 50 mm Hg at a follow up of 1 to 2 years though one also required a surgical valvotomy. The fifth patient died of congestive failure 10 days after balloon dilatation. Of the eight patients treated between one month and one year of age, four are well palliated (one after a second balloon dilatation). There was one procedural death due to an anaesthetic complication. Surgery was performed in three patients: two after a second balloon dilatation and one urgently after valve disruption. Of the 16 patients treated after the first year of life, two had previously undergone a surgical valvotomy. The immediate transvalvar gradients after balloon dilatation fell from a mean of 67 mm Hg (range 40 to 105) to a mean of 27 mm Hg (range 10 to 40). One patient required a further balloon dilatation. There has been no mortality or need for surgery in any of these patients. The Doppler estimated gradients ranged from 22 to 60 mm Hg after follow up from two months to four years.

Balloon dilatation of critical aortic stenosis in neonates is accompanied by a high mortality due to arterial complications and associated left ventricular dysfunction. Presentation beyond the first week of life is associated with a better outcome and prognosis. In patients >1 year of age balloon dilatation is an effective and safe palliative procedure that can delay the need for, and supplement, surgery.

Comparison of balloon dilatation, laser-balloon dilatation and stent implantation for maintaining patency of the arterial duct

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In children with duct dependent cyanotic heart disease, maintenance of patency of the arterial duct by transcatheter techniques, could replace neonatal systemic to pulmonary artery shunt operations. We have evaluated the relative efficacy of balloon dilatation, laser "hot" balloon dilatation, and stent implantation for this purpose in 30 newborn lambs (age 4.4 (1.7) days; weight 4.6 (1.2) kg). In three lambs, it was not possible to recanalise the duct. In seven, balloon dilatation (with 4–10 mm balloons) alone and in two, laser balloon dilatation (2.5 and 3 mm laser balloons) was performed. Stent implantation alone was performed in seven (four with additional balloon dilatation) using balloon expandable or self expanding stents of 4–8 mm diameter, and 11 underwent sequential balloon dilatation and stent implantation with the same size device (4–6 mm). After balloon dilatation alone, the duct size averaged 40–50% of the balloon diameter. Within five minutes of balloon dilatation, however, the duct had either closed or constricted to a diameter of less than 1 mm in four and less than 2 mm in a further two. The only inflation to 10 mm after a poor result at 8 mm ruptured the duct producing tamponade. Laser balloon dilatation alone produced patent ducts of only 1–1.5 mm. Stent implantation produced well defined ducts with diameters of at least 80–90% of the stent diameter. In those undergoing sequential balloon dilatation and stent implantation with similar sized devices, there was a rise in the pulmonary to systemic pressure ratio from 0.31 (0.1) at baseline to 0.41 (0.1) after balloon dilatation and to 0.57 (0.2) after stent implantation ($p < 0.001$). The pulmonary to systemic flow ratio increased from 2.2 (1.0) after balloon dilatation to 3.5 (2.1) after stent implantation ($p < 0.05$). The duct diameter at angiography increased from 0 mm at baseline to 2.1 (1.3) mm after balloon dilatation and to 4.7 (1.0) mm after stent implantation ($p < 0.001$).

Stent implantation with 4–6 mm devices, consistently produces better haemodynamic and angiographic patency of the arterial duct than balloon or laser balloon dilatation alone. Long term studies of its efficacy are warranted.

Long-term results of stent implantation for maintaining patency of the arterial duct

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Stent implantation has been shown to be superior to balloon dilatation in achieving widely patent and regular channels, either as an adjunct to or in place of balloon dilatation, in both peripheral and coronary artery disease. To investigate the possibility that stent implantation into the arterial duct could replace neonatal systemic to pulmonary artery shunt operations we implanted stents (Wallstent, Tower or Palmaz-Schatz) into the arterial ducts of 15 newborn lambs (age 2 to 7 days, weight 3 to 7.3 kg). Within 4 to 10 days of stent implantation the duct was closed or virtually closed in five. In all of these the stents had been

placed so that 1 to 2 mm of the aortic end of the duct had not been stented. In three of these the stents could not be visualised at the time of implantation due to poor radio-opacity (Palmaz-Schatz stents). In one, the duct was barely patent (Tower) and in one the stent had passed through an intimal tear at the aortic orifice (Wallstent). The first was redilated and the second had an additional overlapping stent implanted. Three lambs died within 48 hours of the procedure and in these the duct was found to be patent. In seven lambs (four with Wallstents and three with Tower stents), follow up now extends to 10 months (median 7.5 months; current weight 10 to 60 kg) and in these the ducts have remained patent. In one, who died six months after stent implantation, from unrelated causes, the duct was investigated by angioscopy. The stent in the duct itself was completely covered by a thin layer of endothelium while a 1 mm portion of the stent protruding into the aorta was free from thrombus or neo-endothelium formation. At the pulmonary end a non-occlusive fibrous narrowing was beginning to form.

Arterial duct patency can be maintained in the long term but to achieve this the implanted stents must span the entire duct length. Stent implantation into the arterial duct may become a viable alternative to neonatal systemic to pulmonary artery shunt operations.

Maintenance of ductal patency by percutaneous stent implantation: early experience

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Balloon expandable stainless steel stents (Johnson and Johnson) were deployed in the arterial duct in four neonates with duct dependent circulation. Two had pulmonary atresia with right sided aortic arch and left sided duct and two had left heart hypoplasia. The stents were mounted upon 3.5 to 4 mm (pulmonary atresia) or 7 mm (hypoplastic left heart) diameter balloon angioplasty catheters and were delivered using the femoral venous, femoral arterial, or axillary arterial approach under general anaesthetic. Repeated procedures were necessary to stent the full length of the ducts in pulmonary atresia; two stents (7 mm and 15 mm length) were required in one case and four (one 15 mm and three overlapping 7 mm stents) in the other. In hypoplasia of the left heart two stents were required in one child and a single stent in the other. Complications included guide wire perforation of a pulmonary artery (treated conservatively), cardiac tamponade (treated by pericardicentesis and autotransfusion), and transient loss of cardiac output. Of those with pulmonary atresia one baby died after five weeks of uncertain cause and the second died of pneumococcal septicaemia after nine days. One baby with hypoplastic left heart died two weeks after stenting, due to sepsis and right heart failure and the other is alive and well after one month. At necropsy the ducts were patent and endothelialisation was nearly complete after five weeks.

Stenting of the arterial duct may allow successful maintenance of patency and merits further study.

Effect on overall outcome of the introduction of balloon dilatation of native aortic coarctation in infants and children

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Since May 1990, 33 neonates, infants, and children presenting with native aortic coarctation and normal cardiac connections were considered for percutaneous balloon dilatation. Twenty four subsequently had balloon dilatation of the coarctation but nine were referred for surgery. The outcome in terms of mortality, complications, and recoarctation (assessed by clinical evaluation, Doppler echocardiography, magnetic resonance imaging, and the need for further procedures) in these 33 children (group A) was compared with that in the 21 consecutive children treated surgically for coarctation between January 1989 and May 1990 (group B). There were 16/33 (48%) neonates in group A and 11/21 (52%) in group B. The median age was 26 days and the median weight 3.7 kg for group A and 32 days and 3.6 kg for group B. In 16 neonates in group A, there were five (31%) deaths and in group B, two (18%) neonates died. Two of these deaths in group A were related to balloon dilatation and one to primary surgical repair, whereas in group B, one death was related to surgery. In patients older than one month, there were no deaths in group A and one death in group B occurred at surgical repair of recoarctation and resection of subaortic stenosis. Of the neonates, four (25%) in group A and three (27%) in group B developed recoarctation. Of those patients older than one month, two (12%) in group A and one (10%) in group B developed recoarctation. Three additional patients in group A and one patient in group B have mild recoarctation on magnetic resonance imaging but have not needed any intervention. No aneurysms have been detected by magnetic resonance imaging in either group.

Balloon dilatation is an acceptable alternative to surgical repair of native coarctation in infants and children, but its role in neonates remains controversial. Nevertheless, some older neonates may derive medium term benefit from balloon dilatation.

Malposition of the Rashkind double umbrella as a cause of residual flow after transcatheter occlusion of the arterial duct

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The lateral aortograms obtained before and after implantation of a single Rashkind arterial duct occluder were reviewed in 121 patients. The position of the occluder within the duct, the disposition of its prongs, and any distortion of the duct from its original shape were noted. Twelve cases were identified in which the distal prongs of the occluder distorted the ampulla or body of the duct in such a way as to splint it more widely open than before implantation. In five patients this could be attributed to technical deficiencies but the shape of the duct contributed to malposition in seven. Outcome of the procedure in terms of achieving complete occlusion confirmed by Doppler echocardiography and the requirement for a second occluder was then compared between cases in whom malposition was present and those in whom the occluder position was optimal. Five (42%) of the 12 ducts with malposition were completely occluded compared with

75/109 (69%) of those with optimum occluder position. Moreover, 5/12 (42%) of those with malposition have residual flow beyond four months after implantation compared with only 14/109 (13%) of those with optimum position. Four (33%) with malposition and 10 (9%) without malposition have had implantation of a second occluder.

Malposition of the Rashkind occluder makes a significant contribution to residual patency of the duct. If, in the setting of malposition of the occluder complete occlusion does not occur early after implantation, then persistent residual leak can be predicted and a second device should be implanted.

Factors influencing the late results of transcatheter occlusion of patent arterial duct with an umbrella device

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The influence of the morphology of the arterial duct, the position and size of the umbrella device, and the time after implantation on the incidence of residual patency was investigated in 125 patients who had undergone arterial duct occlusion using the Rashkind device. The shape of the duct, assessed on the lateral aortogram, was classified into one of five categories: (1) broad funnel, (2) short (no ampulla), (3) parallel tubular, (4) tubular with narrow pulmonary end, and (5) complex. 63/125 (50%) ducts were classified as type 1, 14 (11%) type 2, 21 (17%) type 3, 23 (19%) type 4, and 4 (3%) type 5. The duct was classified into one of three categories: (A) ≤ 3 mm, (B) > 3 mm ≤ 6 mm, (C) > 6 mm. The ducts were in category A in 103 (82%), B in 21 (17%), and C in one (1%). The incidence of complete occlusion for each shape and size of the duct was evaluated. For category A, the occlusion rates were: type 1 = 39/53 (73.5%), type 2 = 8/12 (67%), type 3 = 6/13 (56%), type 4 = 17/23 (73%), and type 5 = 2/2 (100%). The rates of occlusion for category B were: type 1 = 5/10 (50%), type 2 = 1/1 (100%), type 3 = 6/8 (75%), type 4 = 1/2 (50%). The single type 1 duct in category C had a residual leak. Of 41 ducts with residual leak, the position of the occlusion device was suboptimal in eight and optimal in 33 and the size of the device was inappropriate in seven. Of 84 ducts with no residual leak at the latest follow up, 32/84 (38%) were completely occluded on the immediate postimplantation aortogram, and 58/84 (69%) were occluded when assessed by Doppler echocardiogram the next day. The remaining 26 (31%) were first assessed as completely occluded between six weeks and two years later (median = six months).

Small ducts are associated with a higher incidence of complete occlusion but duct shape also influences the results. Malposition and inappropriate size of the occluder are important causes of residual leak. There is a continuing incidence of closure of residual patency with time.

Enhanced myocardial resistance to hypoxia after heat stress is dependent on metabolic substrate

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When any living cell is exposed to sub-lethal temperature increase a series of adaptive changes occur which serve to protect that cell from subsequent increases in temperature.

A group of proteins known as the heat stress proteins are the only proteins translated during such stress and play a pivotal role in providing this protection. In the heart a wide variety of insults other than heat stress, such as ischaemia also result in heat stress protein synthesis. In the buffer perfused rabbit heart, heat stress enhances contractile function after ischaemia and reperfusion. The physiological basis for this protection is unknown; however heat stress proteins are known to influence mitochondrial ATP formation and be essential to mitochondrial protein metabolism. This study was therefore designed to determine if the protection associated with heat stress is influenced by the presence of a glycolytic (glucose) or mitochondrial (pyruvate) substrate. Rabbits were heat stressed by raising their temperature to 42°C for 15 min. Twenty four hours later their hearts were removed and papillary muscles mounted isometrically and stimulated at 1 Hz at 37°C. Control papillary muscles were prepared identically but without heat stress. Contractile recovery after 30 min of hypoxia without substrate was examined in four experimental groups and expressed as a percentage of baseline function: Group 1, control perfused with pyruvate ($n = 12$), recovery rates at 30, 60 and 90 mins after hypoxia were 47.1 (2.6)%, 54.8 (4.7)%, and 58.9 (5.4)% respectively; group 2, heat stressed perfused with pyruvate ($n = 12$). Recovery rates at 30, 60 and 90 mins after hypoxia were 60.9 (7.3)%, 75.3 (9.6)% and 84.2 (11.35)% respectively. At each time the differences between these groups was significant ($p < 0.05$, Wilcoxon signed rank). By contrast group 3, control perfused with glucose ($n = 12$) and group 4, heat stress perfused with glucose ($n = 12$), did not differ at any time and were similar to group 2 in terms of recovery. The 72 kD and 65 kD stress proteins were raised in right ventricular tissue from heat stressed groups.

These results suggest that heat stress preferentially increases mitochondrial resistance to hypoxia and reoxygenation whereas protection of glycolytic pathways seems minimal.

Preconditioning with heat stress protects the ischaemic myocardium

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Heat stress and the subsequent expression of stress proteins has been shown to offer protection to the isolated *in vitro* rabbit heart, although no benefit is apparent with an *in vivo* rabbit model. This study was designed to investigate this discrepancy and to ascertain if heating itself has any effect on the blood which could negate the protection derived from myocardial stress protein synthesis. We used an isolated blood perfused rabbit model in which a support rabbit (heat stress or control) perfused an isolated donor rabbit heart (heat stress or control). The heat stress consisted of whole body hyperthermia at 42°C for 15 minutes, 24 hours before the experiment. Donor rabbits were then anaesthetised and their hearts removed. These isolated donor hearts were then subjected to 45 minutes of regional ischaemia followed by 120 minutes of reperfusion. Infarct size was measured with triphenyl tetrazolium chloride and expressed as a percentage of the risk zone (I/R) measured with fluorescent microspheres. Results show that heat stress protects the rabbit heart in the absence of heat stressed blood (control support rabbit perfusing control isolated heart, I/R = 34.7 (3.7)% ($n = 15$) compared

with control support rabbit perfusing heat stressed isolated heart, I/R = 23.5 (3.3)% ($n = 16$) $p < 0.05$). When the support animal has been heated, however, I/R appears greater in both groups (control isolated heart I/R = 44.9 (3.3)% ($n = 12$), $p < 0.05$ *v* control/control and heat stressed isolated heart I/R = 51.9 (7.0)% ($n = 7$), $p < 0.01$ *v* control blood/heat stressed heart). To ascertain if heat stress could limit infarct size in the absence of blood, we repeated the above experiment using isolated hearts perfused with Krebs buffer containing 2% bovine serum albumin; I/R in the control and heat stressed groups were 70.8 (4.3)% ($n = 10$) and 51.5 (5.7)% ($n = 12$) respectively, showing a significant protection in the heat stressed group ($p < 0.05$).

We conclude that although heat stress appears to precondition the heart by limiting infarct size, it also has adverse effects—probably on the blood—that may override any benefit associated with stress protein synthesis.

Myocardial resistance to calcium overload is enhanced by prior heat stress

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When any living cell is exposed to sublethal temperature increase a series of adaptive changes occurs that serves to protect that cell from subsequent increases in temperature. A group of proteins known as the heat stress proteins are the only proteins translated during such stress and play a pivotal role in providing this protection. In the heart a wide variety of insults other than heat stress, such as ischaemia, also result in heat stress protein synthesis. In the buffer perfused rat and rabbit heart, raised heat stress protein associates with an enhanced resistance to ischaemia and reperfusion. This resistance has been attributed to an increase in endogenous cardiac anti-oxidant activity. Our aim was to examine the effect of heat stress proteins on the calcium paradox, which is thought to induce calcium overload injury similar to ischaemia and reperfusion but without oxidant stress. Rabbits were heat stressed by raising their temperature to 42°C for 15 min. Twenty four hours later hearts ($n = 10$), were removed and retrogradely perfused at 37°C with Tyrode's 1.3 mM Ca^{2+} for 15 min, before perfusion with no Ca^{2+} for five min, and finally abrupt reintroduction of 1.3 mM Ca^{2+} . Throughout the experiments hearts were paced via the right atrium at 180 beats per min. Paired control hearts ($n = 10$), sharing the same perfusate as their matched heat stressed hearts, were prepared identically but without heating. Five control and five heat stressed hearts were used for both 65 kD and 72 kD heat stress protein estimation. After reintroduction of Ca^{2+} , left ventricular developed pressure was better preserved in heat stressed *v* control hearts at five min (36.4 (5.4) *v* 20.8 (4.5) mm Hg ($p = 0.02$) respectively) and 10 min (38.3 (5.0) *v* 18.8 (4.1) mm Hg ($p = 0.003$) respectively). In addition creatine kinase release into the coronary effluent was diminished in heat stressed *v* control hearts at one min (10.6 (8.6) *v* 86.4 (33.7) units per min per gm ($p = 0.01$) respectively), and five min (4.9 (3.5) *v* 81.8 (39.6) units per min per gm ($p = 0.03$) respectively). Similar advantages were seen in the heat stressed group in terms of myoglobin release and contracture. Cardiac heat stress protein content for both 65 and 72 kD proteins was raised.

Heat stress seems able to increase cardiac stress protein content and limit myocardial injury associated with a sub-

maximal calcium paradox. This study suggests that the myocardial protein associated with heat stress is not based solely on enhanced anti-oxidant defences.

Impaired immediate vasoconstrictor response to head-up tilt: new insights into the pathophysiology of vasovagal syncope

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Upright tilt testing in the evaluation of unexplained syncope is now accepted as a valuable diagnostic technique. The exact mechanism of neurally mediated syncope, however, and the factors leading to individual susceptibility to orthostatic stress remain obscure. Given that many clinical episodes of syncope occur after comparatively short periods of upright posture, we hypothesised that measurable abnormalities may be present soon after tilting in patients with neurally mediated syncope. The aim of the study was to examine the initial vascular responses to head up tilt in patients with syncope that remained unexplained after clinical and non-invasive evaluation. Forearm blood flow and forearm vascular resistance were measured by strain gauge plethysmography in 53 consecutive patients (mean age 45, range 11–82) with unexplained syncope undergoing tilt testing at 60° for a maximum of 40 minutes. 26 patients (group S) became syncopal (mean time to syncope 18 min, range 5 to 38) and 27 (group N) showed normal responses. Age between the groups was not different and none of the patients had significant structural heart disease, diabetes, or evidence of neuropathy. Supine and after two min of tilt there were no significant differences in heart rate or blood pressure between the groups. After five minutes of tilt the mean arterial pressure was 94 (16) mm Hg in group S and 102 (11) mm Hg in group N ($p < 0.05$). Forearm vascular resistance (in arbitrary units) was well matched between the groups at baseline (group S:36.5 (18) *v* group N:33.4 (15), NS); however, after two min of tilt mean forearm vascular resistance was 55.5 (21.5) in group S and 86.9 (45.5) in group N ($p < 0.02$), and similarly at five min group S:49.9 (18) *v* group N:78.9 (34.3) ($p < 0.01$).

Immediate forearm vasoconstrictor responses to head up tilt are reduced in patients who have neurally mediated syncope even though syncope often does not occur until substantially later. This may explain their susceptibility to postural stress.

Morphology of the cardiac conduction system in patients with dual atrioventricular nodal pathways

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The anatomical substrate for atrioventricular nodal reentrant tachycardia is thought to be within the node or else is composed of pathways in the atrial transitional cell zone. Few histological studies have been reported, none with any convincing evidence of discrete pathways. In this study, seven patients underwent standard electrophysiological assessment of atrioventricular nodal function before cardiac transplantation. A tissue block was removed from each of the explanted hearts. The tissue blocks were sectioned serially and sections included the perinodal region posteriorly extending to the orifice of the coronary sinus. The

sections were studied blind to the electrophysiological findings. The structure of the atrioventricular node was normal in all with minor variations within the atrioventricular system in three cases, within the penetrating bundle in one case, fibrotic origin of the right bundle branch in two cases, and tenuous origin of the left bundle branch in two cases. There was fatty infiltration of the atrial transitional cell zone in four cases. On reviewing the electrophysiological findings, 6/7 patients were found to have dual atrioventricular nodal pathways as defined by a jump of ≥ 50 ms in the antegrade conduction curve with a decrement of 10 ms.

When correlated with the histological findings, no discrete anatomical substrate could be implicated for this electrophysiological phenomenon. The difference between "normal" and "variation of normal" in these cases may be too subtle to be detected by gross morphological findings.

Prevalence of dual atrioventricular nodal pathway physiology in patients without arrhythmias

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The prevalence of dual atrioventricular nodal pathway physiology is not known. It has long been assumed that it provides a substrate for reentrant tachycardias, but its clinical significance in most people is not known. Recent mapping information suggests that the slow pathway may not be sited in the node, but may form part of the nodal input from the atrium. If this is so, dual pathways should be common. Thirteen patients with end stage heart failure, but without either a history of palpitation or documented sustained arrhythmia, were studied. All underwent standard electrophysiological assessment of atrioventricular nodal function using three quadripolar electrode catheters at the time of right heart catheterisation to assess pulmonary vascular resistance. Dual atrioventricular nodal physiology was defined as a jump in the antegrade atrioventricular nodal conduction curve of < 50 ms with a decrement in A1–A2 of 10 ms. Using this standard definition, 10/13 had dual atrioventricular nodal pathways, and seven/13 had two completely discrete atrioventricular nodal curves. Retrograde conduction was present in only four patients, and conduction curves were single in all four. No patient had atrioventricular node reentrant tachycardia induced. One patient had a concealed accessory pathway, and previously unsuspected atrioventricular reciprocating tachycardia was induced.

Thus in this small series of patients without arrhythmias, dual atrioventricular nodal physiology is common, occurring in 77%. In these patients it has had no clinical significance. This pattern, commonly considered an abnormal and potentially pathological variant, may be universal, and may in fact be normal.

Radiofrequency catheter ablation for all forms of junctional reentry: a new, safe, and effective therapy for all age groups

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Junctional reentry tachycardias (JRT), in association with accessory atrioventricular pathways (AV) present at all ages, are disturbing and may be life threatening. Drugs and

antitachycardia pacing offer incomplete protection and selective destruction of accessory pathways (AP) while preserving the AV node has hitherto usually required surgery. Radiofrequency (RF) energy delivered endocardially via steerable catheter electrodes usually causes painless and localised necrosis and was therefore used to treat 28 patients (15 women), mean age 33 (range 7 to 62) with refractory JRT. In 13 patients ablation was performed during their first electrophysiology study. Seventeen patients had the Wolff-Parkinson-White syndrome (12 left sided, two right sided, 2 posteroseptal, and one antero-septal AP), four had concealed left free wall AP, five had typical AV nodal reentry tachycardia (AVNRT), one atypical AVNRT, and one patient had a Mahaim AP. In all patients, ablation of the AP was attempted and for AVNRT, ablation was directed at the slow pathway. Successful ablation of the target pathway was achieved in 22 out of 28 (78.6%) and in 17 of the last 20 (85%) procedures. Failure occurred with three left free wall AP (one concealed) and both posteroseptal AP. Recurrent atrial fibrillation (AF) prevented ablation of one typical AVNRT although one left free wall AP was successfully ablated during AF. Potentials presumed to arise from the AP were recorded in only 15 patients but were always associated with successful ablation. Other electrogram variables (AV interval, AV amplitude ratio, V-delta interval) were not always helpful in distinguishing successful from unsuccessful ablation sites. Loss of pre-excitation within four seconds of delivery of 30 W of RF energy was permanent except in one patient eventually cured by energy delivery above rather than below the mitral annulus. There was no complication related to the ablation procedures and after successful ablation all have remained asymptomatic and well over a mean follow up period of 3.6 (range one to eight) months. Intermittent asymptomatic pre-excitation has returned in one patient after right free wall AP ablation. Function of the AV node was normal in all patients at the end of the procedure although one developed right bundle branch block immediately after ablation of an antero-septal AP.

Radiofrequency ablation appears to be a safe and effective treatment for refractory junctional reentry arrhythmias and should be considered early in their clinical course.

Relation of right ventricular isolation procedures to postoperative ventricular arrhythmias

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In patients with arrhythmogenic right ventricular disease, right ventricular isolation procedures are accepted management options for life threatening ventricular arrhythmias. The aim of this study was to compare the occurrence of ventricular arrhythmias after surgery in patients undergoing total or partial isolation procedures. Signal averaged electrocardiograms were performed in all and the presence of late potentials was related to postoperative arrhythmic events. Late potentials were defined as QRS duration exceeding 120 ms and low amplitude activity within the terminal 40 ms of the signal averaged electrocardiograms with a root mean square value of less than 40 μ V. All patients had late potentials preoperatively. Nine patients who underwent a right ventricular isolation procedure were studied. Four had total right ventricular isolation and

five had disconnection of part (<40%) of the right ventricular free wall. There have been four postoperative ventricular arrhythmias (44%) but all patients are controlled with therapy that had previously been ineffective. Mean postoperative follow up is 29 months. Late potentials were absent after operation in three of the four patients undergoing total right ventricular isolation, and these patients have had no ventricular arrhythmias. The patient with positive late potentials experienced symptomatic runs of non-sustained ventricular tachycardia, abolished by antiarrhythmic therapy (25% arrhythmia occurrence). All five patients who had partial isolation of the right ventricle continue to have late potentials postoperatively and three have developed new ventricular arrhythmias (60%), differing in rate and morphology from their preoperative arrhythmia.

This study shows that total isolation of the right ventricle is associated with fewer postoperative ventricular arrhythmias. The development of new ventricular arrhythmias postoperatively suggests that residual late potentials are important in the genesis. Thus despite its more radical nature, total right ventricular isolation is the preferred surgical approach in patients with arrhythmogenic right ventricular disease.

Plasma fibrinogen, medical history, and prevalent coronary heart disease in the Scottish Heart Health Study

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In the Scottish Heart Health Study plasma fibrinogen was measured in 8824 men and women aged 40 to 59 as part of a cardiovascular survey. It was related to history of high blood pressure, diabetes, stroke, or parental or sibling history of heart disease. Fibrinogen was raised in each case. It was significantly raised after correction for age and smoking, except for diabetes and stroke in women. A case control analysis was carried out defining myocardial infarction and angina from medical history, chest pain questionnaire, and electrocardiogram. Plasma fibrinogen was raised in all categories of myocardial infarction and of angina, compared with controls, in both sexes. After adjustment for age, family history, smoking and drinking, body mass index, blood pressure, total and high density lipoprotein cholesterol, triglyceride, and uric acid concentrations, the odds ratios for disease were calculated across the quartiles of plasma fibrinogen. Odds ratios for myocardial infarction were higher for men than women, were significant in all quartiles of fibrinogen, and showed a significant linear trend. The same was also true for angina. In women none of the odds ratios reached statistical significance after multiple adjustment either for myocardial infarction or for angina pectoris, although some odds ratios were significantly raised when adjusted for age alone.

Incidence of stable angina pectoris in a population survey

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There are no recent data on the incidence of stable angina pectoris in the United Kingdom. The aim of this survey

was to measure incidence prospectively in a selected general practice population. All 102 partners from a stratified random sample of 17 general practices in the City of Southampton were invited, and each agreed to refer all new patients presenting for the first time with suspected non-acute cardiac chest pain to a district general hospital open access chest pain clinic. From a total of 285 referrals between September 1990 and the same month in the following year, 67 (24%) had definite angina and 95 (33%) had definite or possible angina, according to established criteria. From the reported age and sex structure of the practice population of 189 062, the age and sex specific incidence rates per 1000 per year were calculated with 95% confidence intervals (95% CI): men aged ≤ 30 : 0; 31–40: 0.44 (0.09–0.80); 41–50: 0.43 (0.05–0.81); 51–60: 1.32 (0.57–2.07); 61–70: 2.32 (1.27–3.36); and for women in the same age bands: 0; 0.08 (0–0.25); 0.56 (0.11–1.01); 1.05 (0.36–1.73), and 1.01 (0.35–1.67). For definite angina the crude incidence rate for this population was 0.42 (0.32–0.52) per 1000 per annum, and for definite and possible angina it was 0.60 (0.48–0.72). Men aged 61–70 had a fivefold higher incidence compared with the 41–50 age group.

From this random study sample it is estimated that Wessex region population will have 1104 (95% CI 841–1366) new definite angina pectoris cases annually. With prevalent disease estimated at 15 000 middle aged men (the number of women with angina is unknown) in this region current cardiological resources at district and regional level are inadequate for the investigation and treatment of angina pectoris.

A possible new non-invasive diagnostic technique confirms South West Scotland as a high risk area for coronary heart disease

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Scotland has for a long time been recognised as a high risk area for coronary heart disease with parts of Ayrshire amongst the worst affected. Early diagnosis of persons at risk would be advantageous as this would afford greater opportunity for preventative or corrective regimes to achieve success. The development of non-invasive diagnostic techniques is being particularly encouraged (EC Biomedical and Health Research Programme, 1991–4) and this paper presents data on the use of hair calcium (Ca) as a diagnostic aid for coronary heart disease. The technique was developed in Hungary where the proximal end of scalp hair has been analysed for Ca by x ray fluorescence. This has shown that populations normally exhibit a two peaked log normal distribution for hair Ca concentration. The mean concentrations for the low and high groups are significantly different ($P < 0.001$) at 350 and 1500 mg/kg respectively. This technique has also shown that patients suffering from coronary heart disease have considerably lower hair Ca concentrations than comparable healthy controls and that these low concentrations predated admission to their hospital. Examination of hair and aorta Ca concentrations of necropsy samples showed that when hair Ca concentration was high aorta Ca concentration was low with the converse also true. High aorta Ca concentration

was associated with severe alterations in the vessel wall. Samples of scalp hair were obtained from 102 apparently healthy employed male volunteers in Ayrshire and analysed for Ca. These showed a single log normal distribution about a mean of 320 mg/kg. Only one sample had a value (1420 mg/kg) comparable with those found in other studies around the higher peak of 1500 mg/kg.

Thus this Scottish population differed from earlier Hungarian and Japanese studies where the bi-modal distribution was found and from a Zambian one where only high values were recorded. It was similar to two other Hungarian studies on 138 acute myocardial infarction (MI) and 122 post MI patients although even these biased samples were not so one sided. It is apparent therefore that the Ca metabolism of this Scottish population is being uniformly influenced by some unique parameters. What these are and whether they are related to the high prevalence of coronary heart disease in this community can be speculated on but must await further confirmatory studies.

Clinical results of catheter ablation in the United Kingdom and Ireland

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Catheter ablation has achieved an important role in the treatment of refractory arrhythmias. It remains, however, a difficult technique and can be associated with serious complications. To assess the rising use of the technique, The British Pacing and Electrophysiology Group has commissioned a retrospective survey of ablation practice in the United Kingdom. Questionnaires were sent to 50 United Kingdom centres. Forty replies were received. Twenty seven centres (68%) have performed ablation procedures and a further 10 had referred patients for ablation. Fifteen centres agreed to complete an extended questionnaire with details of their clinical results, and 12 have done so to date. Number of patients and success rates using different systems are: *ablation of atrioventricular conduction*: high energy 254 (77%), low energy 67 (73%), radiofrequency 18 (78%), other 16 (56%), total 355 (75%). *Accessory pathway*: high energy 22 (23%), low energy 41 (49%), radiofrequency 84 (68%), total 147 (56%). *Ventricular tachycardia*: high energy 6 (0%), low energy 20 (30%), radiofrequency 2 (0%), total 26 (23%). *Atrial flutter*: low energy 13 (54%), radiofrequency 2 (50%), total 15 (53%). *Modification of av conduction*: high energy 7 (0%), low energy 9 (11%), radiofrequency 21 (86%), collagen 3 (67%), total 40 (53%). Although these results are in some cases disappointing, it should be noted that recent advances in catheter technology and technique have improved clinical results. The introduction of large surface area electrodes for low energy and radiofrequency ablation have increased success rates significantly using both of these energy sources. It is clear that ablation is effective for therapy of accessory pathways or atrioventricular nodal tachycardia, and in creating complete heart block, but remains unsuccessful in the treatment of ventricular tachycardia.

To prospectively assess the clinical efficacy and cost effectiveness of different techniques for ablation, 26 centres have enrolled in a detailed prospective study of ablation in the United Kingdom and Ireland.

Abnormal gap junction organisation in human myocardial ischaemia and hypertrophy

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By raising antibodies to a portion of the cardiac gap junctional protein, connexin 43, and using these antibodies in an immunohistochemical procedure in combination with laser scanning confocal microscopy, gap junctions can be localised, with a clarity not previously possible, through thick volumes of human myocardial tissue. To explore the structural basis for electromechanical dysfunction in chronic myocardial ischaemia and infarction, and myocardial hypertrophy, this technique was applied to study the organisation of gap junctions in ventricular myocardial samples obtained during cardiac surgery. Gap junctions in normal human ventricle are confined to the intercalated disks. The surface density of gap junction in normal human left ventricle is 0.00508 (0.00070) $\mu\text{m}^2/\mu\text{m}^3$ myocardial volume, and right ventricle has a similar density. The border zone of a healed myocardial infarct has a markedly disturbed gap junction organisation with label distributed longitudinally over the cell surface, facilitating possible intercellular electrical propagation in a similarly disorganised manner. In left ventricular myocardium in which there was obvious preoperative exercise ischaemia but no local infarction, and features of hypertrophy on histology, gap junction labelling appeared normally distributed but had a reduced surface density ($p < 0.05$). The hypertrophied left ventricular myocardium from patients with aortic stenosis also had a reduced gap junction surface density ($p < 0.05$). When the larger cell volume of these pathological tissues is taken into account a derived index of gap junctional content per cell shows a significantly reduced level only in ischaemic ventricle compared with normal ($p < 0.05$), suggesting that the reduced surface density of gap junction is a feature of ischaemia, and not simply hypertrophy, in the ischaemic heart.

Gap junctions are a major determinant of myocardial resistivity. These disturbances of their quantity and distribution may account for the abnormalities of impulse propagation and conduction velocities that are recognised in ischaemic and hypertrophied ventricular myocardium, and may contribute to the arrhythmic tendency and mechanical inefficiency of these hearts.

Cellular morphology and basis for conduction in accessory atrioventricular pathways in the Wolff-Parkinson-White syndrome

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Ultrastructural analysis of surgically resected accessory atrioventricular pathways from patients with the Wolff-Parkinson-White syndrome was performed to determine, for the first time, the underlying cellular morphology and basis for conduction in this congenital anomaly. Gap junctions are a determinant of myocardial resistivity (and conduction velocity) and an immunohistochemical technique for identifying connexin 43, the

major protein of cardiac gap junctions, by laser scanning confocal microscopy were performed in addition to standard light microscopy and thin section electron microscopy. Left sided accessory atrioventricular pathways were composed of myocardium of normal working ventricular type with a gap junction organisation characteristic of ventricular myocytes. Right sided pathways, despite normal light microscopic appearances, included strands of myocardium composed of highly abnormal myocytes characterised by: (a) aberrant myofilament organisation comprising prominent Z bands with a lack of A band material, (b) degenerated mitochondria, (c) intact intercalated disk ultrastructure with the usual arrangement of junctions, including gap junctions composed of connexin 43 with a distribution characteristic of ventricular myocardium.

Despite a noticeable absence of contractile apparatus these abnormal cells, which may comprise the entire pathway, have maintained the structures for efficient electrical coupling and therefore rapid conduction velocities.

Augmented cardiopulmonary baroreflex control in patients with neurally mediated syncope

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Patients with neurally mediated syncope can be identified by head up tilt testing but the causes of individual susceptibility to postural stress remain obscure. The accepted mechanism of the vasovagal reaction implicates cardiac afferent neural activity. Minor degrees of ventricular unloading, such as that produced by -10 mm Hg lower body negative pressure, result in muscle bed vasoconstriction mediated by reduction of the normal inhibitory action of cardiopulmonary afferents on central sympathetic outflow. The purpose of this study was to examine the activity of cardiopulmonary baroreceptors in patients who developed neurally mediated syncope on tilt testing. Twenty seven patients (mean age 48) referred for tilt testing for evaluation of unexplained syncope or pre-syncope were studied. All had structurally normal hearts and no evidence of neuropathy or diabetes. Thirteen (group S) had positive reactions (syncope or a fall in systolic pressure to below 50 mm Hg) to 40 minutes of 60° head up tilt and 15 (group N) showed no evidence of a vasovagal response. Forearm blood flow was measured by mercury in silastic strain gauge plethysmography before and after two minutes of -10 mm Hg lower body negative pressure. The groups were well matched for heart rate, blood pressure and forearm blood flow and resistance at baseline. During lower body negative pressure there were no significant changes in heart rate or blood pressure in either group. The increase in forearm vascular resistance (arbitrary units) was mean (SE) 6.4 (1.6) in group N and 17.0 (5.7) in group S ($p < 0.05$). The percentage increase in forearm vascular resistance was 26.1 (7.0)% in the tilt negative patients and 49.8 (8.4)% in those with neurally mediated syncope ($p = 0.06$).

The gain of inhibitory influence of cardiopulmonary receptors is augmented in patients with neurally mediated syncope. This may shed light on the cause of individual susceptibility to orthostatic stress.

Increased vascular resistance in chronic heart failure is not due to ultrastructural changes in the vasculature of skeletal muscle

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Chronic heart failure is characterised by increased systemic vascular resistance, and diminished blood flow to exercising skeletal muscle. The pathogenesis of the increased resistance is not known, and may be due to functional abnormalities or structural changes such as endothelial cell swelling. We have investigated the ultrastructure of the microvasculature. Needle biopsies of the quadriceps muscle were taken from seven men with normal left ventricular function (mean (SD) age 43 (22)). Surgical ablation of accessory pathways was being undertaken in four, and three underwent coronary artery surgery. The findings were compared with those from 10 subjects with New York Heart Association III or IV heart failure (age 44 (12); seven men). Four patients had idiopathic dilated cardiomyopathy, three ischaemic heart disease, and three chronic constrictive pericarditis. Samples were processed for ultra-thin sectioning using ruthenium red as a basement membrane stain, and sections were subsequently stained with uranyl acetate and lead citrate. Electron micrographs were taken of 10 transversely cut capillaries from each specimen. The total cross sectional area and area of the endothelium was measured, and the true diameter was assessed by the short axis diameter. The basement membrane thickness was calculated from the mean of six readings around the periphery of the vessel. The short axis diameter in the two groups was not significantly different (3.37 (0.21) μm , chronic heart failure 3.56 (0.37) μm), nor was the total cross sectional area (11.64 (1.86) μm^2 , chronic heart failure 13.56 (2.78) μm^2) nor was the area of the endothelium (4.90 (1.18) μm^2 , chronic heart failure 6.00 (1.58) μm^2). The mean thickness of the basement membrane was marginally increased in the patients with chronic heart failure when compared with controls (0.31 (0.077) μm v 0.246 (0.047) μm , $p = 0.05$).

In subjects with severe chronic heart failure, the increased resistance in skeletal muscle vasculature is not due to ultrastructural changes in the capillaries nor to endothelial cell swelling.

Early complement and neutrophil activation is associated with failed reperfusion after streptokinase

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An accelerated inflammatory response after ischaemia and reperfusion may have a detrimental effect on myocardial perfusion and myocyte necrosis. After reperfusion early neutrophil infiltration is mediated in part by complement activation. No previous reports have shown very early complement and neutrophil activation in those that do not reperfuse. We have studied the acute inflammatory

response in 17 patients with acute myocardial infarction treated with 1.5 MU streptokinase. Neutrophil activation (specific neutrophil elastase radioimmunoassay) and complement activation was measured (before streptokinase and at 20, 45, 75, and 120 min). Based upon a validated technique of ST analysis, reperfusion occurred in 12 patients. Baseline complement and elastase activities were not raised and were not temporally related to the duration of chest pain. Non-reperfusion was associated with a dramatic early rise in elastase activity at 20 min in three out of five patients (area under the curve 12 651 ($n = 3$) v 3993 ($n = 12$) ng min/ml, $p = 0.01$). These patients tended to have systolic hypotension during the streptokinase infusion (mean 88 mm Hg v 103 mm Hg). Plasma and serum samples showed evidence of early complement activation at 20 min (CH50 214 v 96 units/ml, C3P 18.2 v 44.3 ng/ml reperfused and non-reperfused respectively, $p < 0.05$). In those with reperfusion a delayed modest rise in elastase activity occurred ($p < 0.001$) largely after 45 min.

Neutrophil activation occurs during streptokinase infusion. Early marked activation may identify patients without reperfusion and may be the consequence of an antigen antibody reaction.

Identification of a hypervariable polymorphism within the cardiac β myosin heavy chain gene (MYH7): detection of genetic heterogeneity in families with hypertrophic cardiomyopathy

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Familial hypertrophic cardiomyopathy is an autosomal dominant disorder characterised by ventricular hypertrophy and sudden death in the young. Assignment of the disease locus to chromosome 14q11-12 was established and resulted in the identification of a candidate gene within the limited region—the cardiac β myosin heavy chain gene (MHY7). Subsequently, three mutations in exons 9, 13 and 27 (Tanigawa *et al* 1990; Rosenzweig *et al* 1991) have been detected implicating the role of this gene in the pathology. Genetic heterogeneity has been reported, although the proportion of families where the disease results from mutation within MYH7 has yet to be determined. The identification of a hypervariable intragenic marker would obviously represent an effective means for establishing heterogeneity, even within relatively small nuclear families. We report the identification of a highly informative (CA) n dinucleotide repeat polymorphism within MHY7; eight alleles have been detected to date in normal and affected populations. Genetic linkage analysis carried out in eight nuclear pedigrees has resulted in the detection of recombination events within two unrelated pedigrees, confirming the usefulness of this marker.

No obvious correlation between phenotype and genetic heterogeneity was found.

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Mean platelet volume predicts restenosis after successful coronary angioplasty

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Platelets are anucleate and therefore incapable of protein synthesis. Their protein content and size is determined at the time of thrombopoiesis from megakaryocytes. Larger platelets are more active than smaller ones and contain more granules that store platelet derived growth factor. We postulated that large platelets may have more mitogenic activity. We measured prospectively the mean platelet volume with a resistive particle counter in 47 patients before they underwent single vessel coronary angioplasty. These patients had repeat cardiac catheterisation six months after the angioplasty (range 1.5–eight months) to assess the degree of restenosis at the angioplasty site. Restenosis was determined clinically as recurrent angina or a positive exercise test, or both, and a significant stenosis (defined as a post-angioplasty stenosis of <50% increasing to >50% at follow up). In the non-restenosis group ($n = 23$) the mean platelet volume was 8.0 (0.61) fl compared with 8.6 (0.56) fl in the restenosis group ($n = 24$) ($p = 0.001$). There was no significant difference in platelet count haemoglobin, mean corpuscular volume, or white cell count between the groups. In addition, to determine the biological significance of mean platelet volume in the restenotic process, the angiograms were analysed quantitatively by calliper measurements. The loss in minimal luminal diameter between angioplasty and follow up angiogram was calculated and found to be related to mean platelet volume ($r = 0.56$, $p = 0.016$).

Patients with high mean platelet volumes are thus more likely to develop restenosis after initially successful angioplasty. Megakaryocyte changes may predispose to restenosis.

Relation between myocardial collagen and echo amplitude

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To study the effect of myocardial collagen concentration on the ultrasonic backscatter signal from non-fibrotic myocardium, 25 patients (five women) were studied 355 to 2939 days (1009 (718), mean (SD)) after orthotopic cardiac transplantation at the time of annual cardiac catheterisation and endomyocardial biopsy. Patient ages ranged from 22 to 62 (mean 46 (SD 11)), donor ages were 14 to 47 (25 (8)), and the ischaemic time 90 to 245 minutes (151 (42)). All but four patients were treated with cyclosporine A and azathioprine. All were clinically well with no evidence of rejection. Five patients had angiographic coronary artery disease. Tissue was obtained from endomyocardial biopsies taken at cardiac catheterisation. Hydroxyproline:leucine ratios were used as an indication of total myocardial collagen concentration. Ultrasonic

backscatter was assessed by regional myocardial echo amplitude and studies were performed within the 24 hours before catheterisation. There was a significant correlation between myocardial collagen concentration measured by the hydroxyproline: leucine ratio and septal end diastolic echo amplitude ($r = 0.41$, $p = 0.04$, $y = 3.66x + 4.24$). If the five patients with angiographically documented coronary artery disease were excluded from analysis the correlation was substantially improved ($r = 0.51$, $p = 0.02$, $y = 4.19x + 3.89$). These findings suggest that the collagen concentration of myocardium is responsible for about 20% of the myocardial backscatter signal in nonfibrotic hearts.

This supports clinical studies that show increases in myocardial ultrasonic backscatter in conditions where myocardial fibrosis occurs and also indicates the importance of myocardial collagen concentration in determining the ultrasonic backscatter signal in normal hearts.

Measurement of flow in internal mammary artery to coronary artery grafts by transcutaneous ultrasound

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Quantitative ultrasound assessment of proximal internal mammary artery bloodflow was performed using a 7.5 MHz mechanical sector probe with a 3 MHz offset Doppler echocardiogram in 26 patients between six weeks and 12 months after routine coronary artery grafting that included use of at least one internal mammary artery. Flow was detected in all 19 non-grafted right internal mammary arteries, in 16/26 left internal mammary artery grafts, and in 3/7 right internal mammary artery grafts. The internal diameters of grafted and non-grafted vessels were not significantly different (mean (SD) 2.3 (0.3) mm *v* 2.2 (0.2) mm). The flow pattern, however, in grafted and non-grafted vessels was entirely different. In the non-grafted internal mammary artery flow resembled that in other systemic arteries with a high peak systolic velocity (94.1 (30.8) cm/s) and 70 (7.2)% of volume flow occurring during systole. By contrast, grafted vessels showed a lower peak systolic velocity (56.7 (20.4) cm/s, $p < 0.01$), a higher peak diastolic velocity (47.5 (9.9) *v* 24.7 (7.0) cm/s, $p < 0.01$), and a much greater proportion of flow during diastole (65.5 (6.6)% *v* 30 (7.1)%, $p < 0.01$). Mean total flow was 34.2 (14.5) ml/min in non-grafted vessels, 44.4 (17.6) ml/min in left internal mammary artery grafts, and 35.3 (8.3) ml/min in right internal mammary artery grafts ($p = \text{NS}$). Individual resting flows in left internal mammary artery to left anterior descending artery grafts showed a significant positive correlation (Spearman's $r = 0.746$, $p = 0.04$) with myocardial scores calculated by the Green Lane system from preoperative cine angiograms.

Transcutaneous ultrasonography may provide a simple, non-invasive means of studying adaptation of internal mammary artery grafts as well as studying the physiology and pharmacology of coronary blood flow.

Current indications and complications of transoesophageal echocardiography in children with congenital heart disease

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Transoesophageal echocardiography was performed prospectively in a series of 318 selected infants and children with congenital heart disease, to define the safety and current indications of the technique in the primary diagnosis ($n = 116$), the monitoring of interventional cardiac catheterisation or surgery ($n = 115$), and the postoperative follow up ($n = 87$). Complications were encountered in six patients (1.9%). These included arrhythmias in three and signs of oesophageal bleeding in two. No death occurred. The information obtained by transoesophageal echocardiography was compared with that obtained by praecordial ultrasound studies in all patients, and was graded in one of five categories according to its relevance for patient management. Transoesophageal echocardiography studies were incorrect or misleading in 21 patients (7%). Additional morphological or haemodynamic information of value was obtained in 95 patients (30%). The transoesophageal echocardiography study had impact on patient management in 53 children (17%). Areas of improved insights in the primary diagnosis and for postoperative follow up included venous connections, two atrial septal and chamber morphology, atrioventricular valve and junction morphology, the left ventricular outflow tract, and after a Mustard or a Fontan procedure. In the perioperative period, transoesophageal echocardiography was inferior to epicardial ultrasound in the assessment of lesions involving the ventricular septum, the right ventricular outflow tract and the ventriculoatrial junction, but allowed for continuous monitoring in the early postoperative period. During interventional cardiac catheterisation transoesophageal echocardiography allowed for real time monitoring, exclusion of immediate complications, and haemodynamic evaluation.

Transoesophageal echocardiography is a semi-invasive diagnostic technique with a complication rate of 1.9%. The technique should be considered an integral part in the diagnostic and monitoring approach in children with complex congenital heart disease involving the venous return, the atrial chambers, and the atrioventricular junction. Biplane technology will enhance the value of the technique in the assessment of lesions involving the ventriculoatrial junction and the right ventricular outflow tract.

Role of the signal-averaged electrocardiogram in the prediction of serious arrhythmic events after myocardial infarction in the thrombolytic era

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The ability of three non-invasive tests and simple clinical variables to predict serious arrhythmic events (sudden death and sustained ventricular tachycardia) in the thrombolytic era was studied in 301 hospital survivors of myocardial infarction. Two hundred and five (68%) received intraventricular thrombolytic treatment. Signal-averaged electrocardiograms were performed within the first 48

hours, on day six, and at discharge. Holter electrocardiograms on day 6 and radionuclide ventriculography on day seven to 14 were carried out. Median follow up was 1.03 years. There were 13 arrhythmic events (sudden death 11, ventricular tachycardia two). A late potential on the 25 Hz highpass signal-averaged electrocardiogram at discharge was 64% (95% CI 36–92%) sensitive and 81% (76–86%) specific for arrhythmic events. High grade ventricular extrasystole on Holter electrocardiogram (10 or more ventricular premature complexes/hour, couplets or non-sustained ventricular tachycardia) had a sensitivity of only 38% (12–64%) and specificity of 74% (71–77%) for arrhythmic events. The best single test for prediction of arrhythmic events was left ventricular ejection fraction < 0.4 with 75% (50–100%) sensitivity and 81% (76–85%) specificity. In a multifactor analysis involving both clinical variables and results of the three tests, predictors of arrhythmic events, in rank order, were digoxin treatment at discharge, late potential at discharge, absence of angina before myocardial infarction, and a history of previous myocardial infarction. With the results of the multifactor analysis, a discriminant score was computed which identified a high risk group (12% of the total population) with an event rate of 26% and a low risk group (88%) with a 0.8% event rate.

After myocardial infarction in the thrombolytic era, a combination of clinical and investigative variables, including the signal averaged electrocardiogram result, best identifies a small subgroup at high risk of arrhythmic events.

Chronotropic incompetence can be accurately assessed by analysis of the chronotropic response during early exercise

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The assessment of chronotropic incompetence at maximum exercise is often difficult because of the problems involved in finding the time at which the maximum workload is achieved despite the use of analysis of respiratory gases and estimations of blood lactate. To determine if the chronotropic response at peak exercise (normal range $> 0.8x$ (220-age)) could be predicted from that attained during early submaximal exercise (normal range $> 0.8x$ predicted heart rate), 65 patients with chronic heart failure (New York Heart Association II and III) underwent symptom limited exercise testing (Bruce protocol) with respiratory gas analysis. The predicted chronotropic response was calculated for each stage of submaximal exercise with Wilkoff's formula. All patients were in sinus rhythm and no patient was taking β blockers, calcium antagonists, or digoxin, or had evidence of exercise induced ischaemia. The peak respiratory quotient achieved at maximum exercise was $1.1 (0.1) (59/65 > 1.0)$. Chronotropic incompetence was found at maximal exercise in 8/65 patients, 10/64 at stage 1, 2/33 at stage 2, and 1/12 at stage 3. A strong association ($r = 0.8$, $p = 0.0001$) was found between the overall submaximal chronotropic response and the chronotropic response achieved at maximal exercise (specificity 87.5%, sensitivity 94.6%). Analysis of the chronotropic response achieved at stage 1 of exercise and that at maximum exercise showed a sensitivity of 87.5%, specificity 96.4%, a positive predictive value of 77.7%, and a negative predictive value of 98.2%. Only one false nega-

tive result was found in a patient who achieved a maximal chronotropic response of 80.1%.

This method enables chronotropic incompetence to be accurately assessed during the early stages of submaximal exercise and shows maximal exercise testing is not required. Furthermore this assessment takes into account the workload achieved at each stage of exercise, patient age, and the resting heart rate, and is likely to prove superior to the assessment of chronotropic incompetence at maximal exercise.

Use of magnetic resonance imaging to assess the long-term results of total correction of tetralogy of Fallot

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The purpose of this study was to assess the function and anatomy of right ventricular outflow tract, and pulmonary arteries by magnetic resonance imaging in conjunction with echocardiography in patients who had correction of tetralogy of Fallot 10 years before. Fourteen patients were studied, (eight male and six female) with an age ranging from 13 to 19 years. There were two groups; the first group (eight patients) consisted of patients who had relief of right ventricular outflow tract obstruction with Gore-tex patch, and the second group (six patients) underwent infundibular resection with or without pulmonary valvotomy, without outflow tract patch. Right ventricular dimensions were assessed using contiguous gradient echo images. In all patients the right ventricle was dilated and the average ejection fraction was 50% (6). The regurgitation fraction and gradient across the pulmonary valves were assessed by phase encoded flow mapping. The results corresponded with echocardiography. There were four peripheral pulmonary artery stenoses which were not detected by echocardiography. There were three other associated cardiac anomalies.

We found the magnetic resonance imaging allowed quantitative and anatomic insight of the heart in the long term follow up of patients who had correction of tetralogy of Fallot, thus supplementing the clinical and echocardiography evaluation.

Complexity, results, and complications of the first 1000 consecutive percutaneous transluminal coronary angioplasty (PTCA) procedures in a regional centre

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Analysis of the angioplasty database in the Wessex Cardiac Centre has been undertaken for the first 1000 consecutive angioplasty procedures (1983 to mid 1991) to find changes in procedure complexity, primary angiographic success rate, and the incidence of complications. Mean age for the series was 55.9 (range 28 to 83, SD 9.6), 808 (80.8%) patients were men, 200 patients (20%) had undergone previous coronary artery bypass grafting, and 51 (5.1%) patients had received thrombolysis before intervention. Procedural complexity increased with experience. Balloon

dilatation was attempted in 1385 lesions (mean 1.4/patient, range 1 to 4), of which coronary graft angioplasty accounted for 120 lesions (8.7%). Comparing the first 500 with the second 500 patients, single vessel dilatation was undertaken in 411 and 334 patients ($p < 0.001$), multi-vessel dilatation in 67 and 97 patients ($p < 0.02$), and occlusions (TIMI grade 0) in 22 and 69 patients ($p < 0.001$) respectively. Overall angiographic success rate was 83.6%, complete success 77.9%, partial success (dilatation of some but not all lesions attempted) 5.7%, failure 16.4%. Significant differences occurred in the angiographic success rate in the different sub-groups varying from 84.6% for single lesion dilatation to as low as 35.6% for chronic occlusions. The angioplasty was uncomplicated in 903 (90.3%) patients, seven patients died while inpatients (early mortality 0.7%), emergency coronary artery bypass graft was required in 41 patients (4.1%), myocardial infarction occurred in 41 patients (4.1%) (Q wave 31, non-Q wave 10). In the second 500 patients there was one death (early mortality 0.2%), seven patients required emergency coronary artery bypass graft (1.4%) ($p < 0.001$ compared with the first 500 patients), and 12 patients sustained a myocardial infarct (2.4%) (Q wave 7, non-Q wave 5) ($p < 0.01$).

Thus despite an increase in procedural complexity, the incidence of complications has fallen with experience.

Platelet activation: an important side effect of contrast media of relevance to coronary angiography and intervention

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Platelet activation is central to the initiation of restenosis after coronary angioplasty. The main stimulus to platelet activation is believed to be the traumatised coronary artery wall resulting from balloon dilatation. Other stimuli, however, may be important. There is evidence that contrast media may generate thrombin when mixed with whole blood. Since thrombin is a potent stimulus of platelet activation and degranulation, a study was performed to establish the effect of contrast media on platelet activation. Ionic (Urografin) and non-ionic (Omnipaque) contrast media were each added to equal volumes of blood from five normal volunteers and incubated for one minute. The platelets were then analysed for expression of two granule membrane antigens expressed on the platelet surface only after degranulation; namely the GMP140 antigen of the alpha granules and the GP53 antigen of the lysosomal membranes. Five μ l of each sample was incubated with fluorochrome labelled anti-GMP140 and anti-GP53 and analysed in Coulter Epics II Flow Cytometer. This whole blood system does not involve the separation of the platelets and thus avoids artifactual activation during preparation. Considerable platelet degranulation occurred in the blood incubated with Omnipaque, 47.4% (8.5) (mean (SD)) expressed GP53, and 69.2% (9.6) expressed GMP140. When incubated with Urografin, only 16.6% (8.7) expressed GP53, and 17.0% (9.4) expressed GMP140. Control samples with no contrast media but incubated under the same conditions with an equal volume of normal saline showed no activation; 0.14% (0.11) of these platelets expressed GP53, and 1.6% (0.3) GMP140. The differences seen were highly statistically significant.

These findings have important implications in the choice of contrast media used during coronary angioplasty; a situation where endothelial cell damage occurs in response to balloon inflation. Contrast induced platelet degranulation in this microenvironment could lead to further release of platelet derived growth factors, vasoactive substances, and haemostatic proteins that may influence rates of both acute occlusion and coronary restenosis.

Impaired myocardial microvascular function in patients with coronary occlusive disease after cardiac transplantation

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Coronary occlusive disease is the major long term problem after cardiac transplantation. It affects both proximal and distal coronary vessels and is therefore difficult to assess angiographically. Coronary flow reserve measurements offer a potentially improved method of monitoring this disease. Coronary flow reserve was assessed in seven patients with chest pain (controls) with normal coronary anatomy, and 60 patients between three months and 10 years (median 4.5 years) after cardiac transplant. A Doppler flow probe was inserted into the proximal left anterior descending coronary artery in each patient and a maximally vasodilating dose of intracoronary papaverine was given. Twenty five transplant patients had angiographic evidence of minor coronary occlusive disease (mean percentage stenosis diameter 23% (6%)) in a proximal coronary vessel (group 1), with 12 of these in the left anterior descending coronary artery (mean stenosis diameter 24% (8%)). The remaining 35 transplant patients had normal coronary angiograms (group 2). Coronary flow reserve was defined as the ratio of the peak flow velocity achieved to the resting blood flow velocity. Group 1 patients had an impaired coronary flow reserve (2.6 (1.1), Student's *t* test) compared with control patients (3.9 (0.4), $p = 0.005$), group 2 patients (3.9 (1.0), $p < 0.001$). No other variables were associated with a reduction in coronary flow reserve. Mean resting flow velocity was similar in all three groups (controls—7.4 cm/s (4.6), group 1—6.9 cm/s (5.9), and group 2—7.4 cm/s (4.8)). Mean peak flow velocity response to papaverine was reduced in group 1 patients (16.8 cm/s (13.5)) compared with group 2 patients (27.7 cm/s (16.4), $p < 0.001$), and controls (28.4 cm/s (15.4), $p = 0.002$). Coronary flow reserve and the peak flow response to papaverine are impaired in cardiac transplant patients with minor proximal coronary stenoses.

Disturbance of cardiac microvascular function contributes to the late morbidity and mortality found in cardiac transplant patients with coronary occlusive disease.

Fast-track coronary angioplasty in patients with chronic stable angina

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In patients with chronic stable angina pectoris coronary angioplasty is usually performed as a deferred elective procedure often requiring another hospital admission. Modern digital cardiac imaging equipment now allows high

quality on the spot analysis of coronary artery lesions such that immediate decisions can be taken on the suitability for angioplasty treatment. This study compares the outcome of treatment of two groups of patients with chronic stable angina pectoris: those who were offered immediate (fast-track) coronary angioplasty after routine diagnostic coronary arteriography (group A), and those in whom coronary angioplasty was deferred because of more extensive and complex disease (group B). A total of 495 patients (73 vessels) were treated in this study, enrolled over a 29 month period. The primary success rate in group A ($n = 129$, mean age 57.3; vessels treated per patient 1.35) was 95.4%. There was no inpatient mortality and no referral for emergency coronary artery bypass surgery. One patient required emergency stent implantation (Palmaz-Schatz) for an occlusive dissection. In group B ($n = 366$, mean age 57.8, vessels treated per patient 1.36) the primary success rate was 90.9% (NS). Seven patients (1.9%) required emergency coronary artery surgery and three patients died during the procedure (0.8%). The median additional time required for angioplasty in group A was 27 minutes and this was not considered to be disruptive to other planned procedures within a diagnostic session.

Follow on coronary angioplasty after routine diagnostic coronary arteriography in selected patients with chronic stable angina is a safe procedure particularly if stent back up is available. This strategy reduces waiting list times for coronary angioplasty and increases the cost efficiency of the procedure.

Should mild coronary stenoses be dilated?

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It is not clear whether mild coronary stenoses (<60%) should be dilated at the time of percutaneous transluminal coronary angioplasty to a more severe lesion. We report on 150 patients who had a mild (40–60%) coronary stenosis in a large epicardial coronary artery at the time of percutaneous transluminal coronary angioplasty to a significant (>70%) lesion in another vessel. Patients with total occlusion, previous angioplasty, or coronary grafts were excluded. One hundred and twenty six men, mean age 55 (39 to 76), and 24 women, mean age 58 (46 to 73) were studied. The primary artery dilated was the left anterior descending in 55%, the right in 27% and the circumflex in 12%. In 125 patients only the primary stenosis was dilated (group I). In 25 patients both stenoses were dilated (group II). Both groups had similar pre-angioplasty symptoms and severity of stenosis. Mean follow up is 3.5 years for group I and 3.6 years for group II. Forty three patients have relapsed (29%), 39 in group I and four in group II. In group I relapse was due solely to progression of the mild stenosis in only four patients (3%). In the other cases relapse was due to restenosis at the primary site or to a new lesion. In group II relapse was due to restenosis at the site of mild stenosis in one case only (4%) (NS).

We conclude that mild coronary stenoses should not be dilated at the time of PTCA to a more severe lesion as very few patients will go on to have symptoms from progression of the mild lesion. We disagree, however, with previous suggestions that dilating mild lesions leads to severe recurrence at the same site.

Omniflex or Magnarail for total coronary occlusions?

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Fifty patients were enrolled in a prospective randomised study to evaluate two angioplasty systems in percutaneous transluminal coronary angioplasty of total coronary occlusions. The age of occlusion could be estimated from previous angiography, a recent myocardial infarction, or a change in anginal symptoms. The mean duration of occlusion was 4.8 months (range two weeks to 10.5 months). Twenty five were initially allocated the Magnarail and 25 the Omniflex as the initial system. The protocol allowed a total of 20 minutes screening time with the initial system before crossover to the other system. The procedure was abandoned if the second system was unsuccessful after a further 20 minutes screening. The primary success for the Magnarail was 64.0% ($n = 16/25$) and for the Omniflex, 56% ($n = 14/25$) (NS). The mean screening time (SD) for successful procedures was 9.3 (14.8) min (Omniflex) and 7.6 (12.2) min (Magnarail) (NS). The additional system was employed in 12 instances of initial failure. This was successful in six instances improving the overall success rate to 72%. The Magnarail succeeded in 62.5% ($n = 5/8$) of Omniflex failures whereas the Omniflex succeeded in 25% of primary Magnarail failures ($n = 1/4$) (NS). In eight instances of failure with the primary system the operator did not proceed with the alternative system. Generally this was due to the presence of a large intimal dissection (6/8) that was induced by the Magnarail in five. The primary success for the Omniflex in left anterior descending coronary artery occlusions was 81.8% ($n = 9/11$) compared with 55.6% ($n = 5/9$) with the Magnarail ($p = 0.04$). The Magnarail was more successful in right coronary artery lesions, however; 72.7% ($n = 8/11$) *v* 37.5% ($n = 3/8$) ($p = 0.04$).

Thus both systems appear useful in angioplasty of coronary occlusions; the Magnarail for more tortuous right coronary artery lesions and the Omniflex for the straighter anterior descending coronary artery occlusions of the left.

Safety, efficacy, and patient toleration of a new inflatable device for compressing the femoral artery after cardiac angiography?

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Bleeding and haematomas are not uncommon after manual compression of the femoral artery after cardiac catheterisation. In this prospective randomised study a new pneumatic compression device ($n = 30$) was compared with manual compression ($n = 37$) by the cardiologist. Both groups were comparable for age, sex, current treatment with aspirin and warfarin, diameter of the arterial sheath, previous procedures via the same artery, procedure duration, blood pressure, and bleeding or presence of haematoma before arterial sheath removal. Patient discomfort was assessed as none 84% *v* 75%, mild 13% *v* 19%, moderate 3% *v* 3%, or severe 0 *v* 3% for the pneumatic *v* manual group respectively. The mean manual compression time was 13.1 (4.1) minutes. Bleeding after compression (5 *v* 2 patients, pneumatic *v* manual, NS) was successfully

treated by reinflation or manual compression respectively. Significant haematomas (diameter > 10 cm) occurred in 3% (pneumatic) and 11% (manual) of patients (NS). None of the haematomas exceeded 20 cm in diameter. Haematoma before sheath removal was reduced in three patients by pneumatic compression.

Pneumatic femoral artery compression is at least as good as manual compression, is safe, easy to apply, and reduces staff involvement without increasing patient discomfort.

Collagen plug for femoral arterial haemostasis after cardiac catheterisation

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Femoral arterial morbidity has increased with the advent of interventional cardiology. This may be related to the time the arterial sheath is in situ, the larger catheter size, and concomitant anticoagulant treatment. Coronary stenting is associated with 10–20% incidence of femoral bleeding complications. We have investigated the efficacy and safety of immediate sealing of the puncture site using 180 mg of purified bovine collagen immediately after the procedure. At the end of the procedure the collagen was administered via a prototype applicator onto the femoral artery entry site without interruption of anticoagulant treatment. Inadvertent introduction of collagen into the arterial lumen was avoided by a colour coded blunt tip probing device designed to measure the skin to artery distance. Forty nine patients undergoing percutaneous transluminal coronary angioplasty and anticoagulated with heparin, aspirin, and dextran were compared with 21 patients undergoing diagnostic coronary arteriography on aspirin only. Femoral arterial sheaths were removed in the catheterisation laboratory when the activated clotting time was 412 (177) (mean (SD)) in the angioplasty group and normal in the angiography group. The manual compression time was 9.1 (10.2) min in the angioplasty group and 3.9 (1.2) min in the angiography group. Delayed bleeding occurred in one patient, and one patient who had undergone coronary atherectomy required surgical revision of the femoral artery due to plaque dislodgement. Ten patients had coronary stents implanted: there were local bleeding complications in one patient.

The collagen plug proved to be safe, simple to use and secured haemostasis quickly. These findings may have important implications for interventional procedures and for early mobilisation after routine catheterisation.

Complementary roles of biplane transoesophageal and precordial echocardiography in evaluating patients undergoing balloon dilatation of the mitral valve?

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To find whether transoesophageal echocardiography (TEE) would provide important new information on patients undergoing percutaneous balloon dilatation of the mitral valve, that could not be obtained by transthoracic echocardiography (TTE), 47 consecutive patients (mean

age 59 (14) years) were prospectively studied by both TTE ($n=47$) and TEE ($n=44$, 33 biplane, 11 single plane) immediately before balloon dilatation and 24 hours afterwards. Mitral valve leaflet morphology, the subvalvar apparatus, mitral regurgitation, and the presence of atrial thrombus were specifically examined. Excellent images were provided by TEE in all patients whereas five patients could not be imaged satisfactorily by TTE. In echogenic patients mitral leaflet thickness, calcification, mobility, and the subvalvar structures could be assessed equally well by both techniques but evaluation of valve orifice and commissures was better achieved by parasternal short axis imaging. Transgastric long axis TEE views (potentially the optimal TEE imaging plane for mitral valve leaflet and sub-valve morphology) could be obtained in only 20/47 patients. Atrial thrombus was diagnosed in eight patients by TEE, and was localised to the appendage in two, and to the main cavity in six; in only one case, (a large thrombus), was this detected precordially. Whereas thrombus identification was possible using either the transverse or longitudinal plane, accurate localisation of thrombus to outside the appendage required longitudinal imaging; the anterior and superior atrial wall was involved in four patients and the posterior wall in one patient. The sixth patient had only a single plane TEE study. Valvotomy was cancelled in three of the eight patients on the basis of the TEE thrombus identification. Before balloon dilatation, TEE and TTE assessments on mitral regurgitation were concordant but after dilatation TEE was superior at evaluating patients with severe mitral regurgitation ($n=3$). Colour flow mitral regurgitation jets were not seen precordially in 2/3 patients whereas TEE identified both the jets and the actual leaflet tears in 2/3 patients examined.

Thus, TEE seems essential for all patients for whom balloon dilatation of the mitral valve is planned because of its superior ability to detect atrial thrombus, compared with TTE. In echogenic patients, mitral morphology, especially the orifice and the commissures, are better assessed from the precordium. After dilatation, the main value of TEE lies in assessing complications, in particular severe mitral regurgitation and its underlying aetiology.

Long-term outcome of the pulmonary autograft operation for aortic valve disease

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Between 1967 and 1984, 149 patients aged 11 to 56 (mean 33) had a pulmonary autograft operation for aortic valve disease at the National Heart Hospital, London. The pulmonary valve was replaced by an aortic homograft in 131 and with other valves (fascia lata, xenografts, and pericardial tubes) in the rest. Eighteen operative deaths (within the first three months) occurred, all before 1973. There were 35 late deaths due to pulmonary autograft regurgitation (four), myocardial failure with intact valves (seven), sudden (seven), reoperation (eight) and other (six). Pulmonary autograft regurgitation was serious in 28 (21%), requiring reoperation in 24. It was due to technical (operative) malposition in 18, endocarditis in four on previously trivial regurgitation, one dehiscence from the only strut and another "rheumatic." No obstruction or degenerative cusps change was identified. Trivial pulmonary

autograft regurgitation was noted from the first year in 36 (27%) and developed after three to 13 years in a further 10. On the right side all fascia lata valves failed and 12 homografts were replaced one to 17 years later. The high incidence of sudden deaths may be attributable to poor techniques of myocardial preservation in the early days. The cumulative survival proportion for hospital survivors at 10 years is 88% (9.6) ($n=84$) and 57% (20) ($n=12$) at 20 years. The event free proportion in those with homografts is 69% at 10 years and 45% at 20 years. The event free proportion for endocarditis at 20 years was 87% (12).

There has been no calcification, stenosis, or cusp degeneration, nor associated haemolysis or emboli. Technical problems with the placing of the autograft and length of operation were overcome after the first 50 cases. Despite the complexity of the surgery and 10% failure of the right sided homograft in 15 years, the pulmonary autograft offers an excellent and durable aortic valve replacement for young patients and appears to have the capacity to remain little changed or unchanged by the passage of time.

Echocardiographic restenosis after successful balloon dilatation of the mitral valve?

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Follow up echocardiography was reviewed in 32 patients after successful balloon dilatation of the mitral valve to assess the echocardiographic incidence of restenosis. Successful dilatation was defined as a gain in mitral valve area of $>25\%$ and a final valve area of $>1.5\text{ cm}^2$, and echocardiographic restenosis was defined as a loss of $>50\%$ of the initial gain and a decrease in mitral valve area to $<1.5\text{ cm}^2$. Echocardiography was performed one year after dilatation. In all patients balloon dilatation of the mitral valve was performed using the Inoue balloon. Initial dilatation resulted in a considerable increase in mitral valve area (mean (SD) 1.0 (0.3) pre v 1.9 (0.4) post, $p < 0.001$). Paired analysis indicated a significant reduction in mitral valve area at one year (1.6 (0.4), $p < 0.001$). Echocardiographic restenosis was present in 8/32 (25%) at one year. After dilatation mitral valve area was significantly lower in the eight patients with restenosis compared with the non-restenotic group (1.6 (0.2) v 2.0 (0.4), $p < 0.01$), whereas after dilatation end diastolic mitral valve gradient and left atrial pressure were similar in the two groups. Echocardiography before dilatation showed considerable valvar and subvalvar calcification or both in 6/8 patients with restenosis compared with 7/24 without restenosis ($p = 0.03$). Of the eight patients with echocardiographic restenosis four underwent mitral valve replacement, two had repeat dilatation and two were treated medically because of lack of clinical symptoms.

Mitral valve area falls significantly in the first year following balloon dilatation of the mitral valve. The echocardiographic restenosis rate one year after successful dilatation is 25%, and a proportion of these patients will have mild symptoms and may be treated conservatively. After dilatation invasive parameters fail to predict restenosis but patients with restenosis do have significantly increase valvar and subvalvar calcification and have less improvement in mitral valve area immediately after balloon dilatation of the mitral valve.

Is thromboembolic risk reduced by balloon dilatation of the mitral valve?

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Spontaneous echo contrast within the heart has been shown to be a marker of thromboembolic risk. This study was undertaken to find the echocardiographic and haemodynamic factors associated with spontaneous echo contrast in patients with severe mitral stenosis, and to assess what, if any, effect balloon dilatation of the mitral valve had on these factors. Forty seven consecutive patients (mean age 59 (14)) were studied prospectively with transthoracic and transoesophageal echocardiography both immediately before dilatation and 24 hours afterwards. Thirty five were in atrial fibrillation (AF) and 12 in sinus rhythm (SR). Echocardiographic and Doppler measurements were: left atrial volume (ellipse method), mitral valve area with both planimetry and Doppler methods, mean transmitral gradient and velocity profiles of blood flow within the left upper pulmonary vein. Haemodynamic measurements were: cardiac output (Fick) and direct mean left atrial pressure, mitral valve area (Gorlin), and transmitral gradient. Spontaneous echo contrast in the left atrium was detected by transoesophageal echocardiography only. It was found in all patients in AF but in only two patients in SR. Eight patients, all in AF, had atrial thrombus. Univariate analysis showed AF ($p < 0.001$), age ($p = 0.003$), left atrial volume ($p = 0.005$), and peak systolic pulmonary vein flow velocity (PSPVFV) ($p = 0.008$) to be predictors of spontaneous echo contrast. There was no significant association with cardiac output, mitral valve area, transmitral gradient, or mean left atrial pressure. Thus patients with spontaneous echo contrast beside being in AF, were older, had larger atrial volume, and had lower PSPVFV, than those without. Multiple regression analysis showed AF to be an independent predictor of spontaneous echo contrast. Thirty nine patients were suitable for and underwent balloon dilatation of the mitral valve. Mean cardiac output, Gorlin mitral valve area, and PSPVFV increased by 24% ($p < 0.001$), 92% ($p < 0.001$), and 11% (NS) respectively. Mean left atrial volume decreased by 16% ($p = 0.001$). Spontaneous echo contrast remained unchanged in all patients except three (one in SR and two in AF) in whom the intensity apparently diminished.

Thus AF is the single most powerful determinant of spontaneous echo contrast in patients with mitral stenosis and dilatation has no immediate effect on spontaneous echo contrast in almost all patients. Thromboembolic risk therefore appears to be unaltered by balloon dilatation of the mitral valve.

The incidence and prognosis of congenital aortic valve stenosis during childhood and into early adult life

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Congenital aortic valve stenosis occurred in 239 patients (155 male, 84 female) born in the Merseyside area between 1960 and 1990, giving an incidence of 4.5 per 10 000 live births. The median age at presentation was 16 months (range 0 to 20 years). Stenosis was mild at presentation in 77% of patients, moderate in 13.8%, and critical in 9.2%.

Two hundred and thirty two of the 239 patients were traced. The median duration of follow up was 9.2 years (range 1 to 28 years). Sixty patients underwent 81 operations for aortic stenosis with a reoperation rate of 30.2%; 17 operations were for aortic valve replacement. Aortic regurgitation occurred in 55 of the surviving patients, a further nine operations were performed for severe aortic regurgitation. There were no sudden deaths. The mortality for the whole group was 16.7%. Actuarial and hazard analysis showed that only 5% of patients who presented with moderate aortic stenosis were free of significant events (operation, balloon dilatation of the valve, endocarditis, or death) after 20 years of follow up, compared with 69% of those who presented with mild stenosis.

An accurate assessment of the severity of aortic valve stenosis at presentation provides a reliable guide to the prognosis into early adult life.

Pulmonary autograft in aortic position (Ross operation): an initial experience

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The use of pulmonary autograft in aortic valve replacement is now in its third decade and is gaining wider acceptance as the problems of prosthetic valves become manifest. These are the initial results of the Ross operation from January 1990 to December 1991 in 17 patients with aortic valve disease. All 17 patients had aortic regurgitation except one who had severe stenosis. There was associated endocarditis with aortic root abscess in three patients, one of them was a child of 18 months with fungal endocarditis from congenital immune deficiency. The right ventricular pulmonary artery continuity was reestablished with a cryo preserved aortic homograft in one, cryo preserved pulmonary homograft in 12, antibiotic preserved fresh pulmonary homograft in two, synthetic valved conduit in one, and by direct connection in one. Associated procedures were relief of supraaortic stenosis using pulmonary autograft in one and mitral valve repair in two patients. There was no mortality. All 17 patients are either in New York Heart Association grade II or asymptomatic. In this short follow up period there have been no valve failures, thromboembolic episodes, or infective endocarditis. Echocardiographic follow up shows 1+ aortic regurgitation in all patients, the systolic gradients ranged from four to 36 mm of mercury with a mean of 12.

The limitation of homograft supply to reestablish right ventricle to pulmonary artery continuity restricts this time proven procedure that would otherwise find greater usage.

Echocardiographic and clinical features are inadequate guides to the management of patients with the Marfan syndrome

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Acute aortic dissection accounts for a high mortality at a young age in the Marfan syndrome. Common practice is to undertake elective surgery in those patients whose aortic root diameter exceeds 5.0 cm. The objective was to ascertain whether clinical and echocardiographic data discrimi-

nate between patients with Marfan syndrome at high and low risk of aortic dissection sufficiently well to determine who should undergo elective aortic surgery. One hundred and forty eight patients satisfied the international diagnostic criteria for Marfan syndrome; the results of detailed physical examination and echocardiographic measurement of aortic root diameter were available for 113 people. Patients were categorised in terms of cardiac outcome into four groups: (1) well ($n = 95$); (2) acute aortic dissection ($n = 11$); (3) elective aortic valve or root surgery ($n = 5$); (4) death from other causes ($n = 2$). Comparisons were made between groups 1 and 2, as the untreated outcome in groups 3 and 4 is unknown. Figures are given as absolute numbers or as mean (SD). No significant difference between the two groups was detected in age (32.9 (13.1) *v* 37.2 (12.3) years), sex (51.44 *v* 7.4 males:females), or height (181.4 (9.3) *v* 188.3 (10.1) cm). The aortic root diameter at latest examination was significantly higher in group 2 (5.1 (1.3) cm *v* 3.7 (0.9) cm, $p < 0.005$). The degree of overlap in aortic root diameter, however, between the two groups was such that no value distinguishes a group of patients at high risk of dissection with sufficient sensitivity and specificity to be the sole determinant for elective surgery, with its attendant risks. The aortic root diameter exceeded 5.0 cm in only half of group 2, but a lower cutoff value would involve operating on a large proportion of patients in group 1. In three cases, furthermore, where echocardiography had been performed both before, and at the time of dissection there was no significant increase in aortic root diameter between the two measurements.

The risk of aortic dissection is higher in those patients with an increased aortic root diameter. Clinical features and aortic root diameter alone, however, are inadequate to determine who should undergo elective surgery, and acute dissection may occur in the absence of a rising aortic root diameter.

In vivo detection of endothelial dysfunction in the pulmonary circulation of children with congenital heart disease

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Endothelial function has a key role in the control of vascular tone and reactivity. To investigate whether endothelial dysfunction occurs early in children at risk of pulmonary vascular disease (PVD), we studied the response of the pulmonary circulation to graded infusions of acetylcholine (ACh, an endothelial dependent dilator) and to nitroprusside (NP, a dilator not dependent on endothelial function) in 26 children aged three to 16 years. Nine had normal pulmonary haemodynamics (controls), eight had established PVD, seven had left to right shunts resulting in increased pulmonary flow (Qp) with normal pulmonary pressure (Pp) and two had unrestrictive ventricular septal defects with increased Qp and Pp but normal pulmonary resistance (Rp). Intra-arterial flow velocity was measured in a lower lobe segmental vessel using a Doppler catheter, and vessel diameter was measured by quantitative angiography. In the controls, there was a dose dependent increase in flow velocity in response to ACh (97 (7)% after 10^{-6} mol/l ACh), and an increase of 53 (10)% in response to NP. By contrast, in patients with PVD the response of flow velocity to ACh (33 (7)%, $p < 0.01$) and to NP (7 (23)%, $p < 0.01$) were both impaired. In the patients with increased Qp and normal Pp there was an impaired

response to ACh (49 (8)%, $p < 0.01$), but response to NP was preserved (43 (9)%, $p > 0.20$), indicating endothelial dysfunction. The two subjects with increased Qp and Pp but normal Rp had impaired responses to ACh and NP. Arterial diameter was unchanged during ACh infusion in all subjects, and only increased modestly in response to NP (≤ 10 %), indicating that the major site of action of both agents is distal to the segmental pulmonary arteries.

Endothelium dependent pulmonary artery relaxation in vivo is impaired in young patients with increased pulmonary flow secondary to congenital heart disease, even in the presence of normal pulmonary resistance. Such impairment may be an important early event in the pathogenesis of pulmonary vascular disease.

Regulation of coronary artery tone by nitric oxide in humans: different role in epicardial and resistive vessels

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Eleven patients (mean age 47, range 28 to 61, seven women) with normal epicardial coronary arteries were studied. All medication was discontinued > 48 hours before the study. Femoral artery blood pressure (BP) and the surface electrocardiogram were monitored continuously. Coronary artery diameter was measured using quantitative angiography. Coronary sinus oxygen saturation (CSO_2) was measured continuously using a fiberoptic catheter in seven patients. All infusions were given intracoronary at 2 ml/min via the diagnostic angiography catheter. In the first two patients studied, N^G -monomethyl-L-arginine (LNMMA), a specific inhibitor of nitric oxide synthesis, was given in low doses (0.1 to 5.0 μ mol/min) into the right coronary artery, and no change in vessel diameter was found. Neither patient developed clinical nor electrocardiographic evidence of ischaemia. These two patients were not included in the final analysis. In the subsequent nine patients, LNMMA was infused at higher doses (4 , 10 , and 25 μ mol/min, each for 5 min) into the left coronary artery. In five patients, incremental doses of acetylcholine (ACh) were infused (1 , 10 , and 100 nmol/min, each for 3 min) before and after the LNMMA infusion. Finally, in all patients, sodium nitroprusside was infused to reverse the effects of LNMMA. No patient developed myocardial ischaemia. The heart rate and BP remained unchanged. LNMMA, compared with the control saline infusion, caused a concentration dependent fall in CSO_2 from mean (SD) 39 (8) to 35 (8)% ($p = 0.035$) at 25 μ mol/min LNMMA, and a reduction in distal left anterior descending coronary artery (LAD) diameter from 1.68 (0.26) to 1.58 (0.20) mm ($p = 0.035$) at 25 μ mol/min LNMMA. Proximal LAD diameter remained unchanged, 3.10 (0.62) *v* 3.05 (0.63) mm ($p = NS$). ACh, compared with the control saline infusion, caused concentration dependent dilatation of distal and proximal LAD before (distal: 1.98 (0.33) *v* 1.63 (0.20) mm, $p = 0.04$; proximal: 2.93 (0.62) *v* 2.51 (0.42) mm, $p = 0.035$, ACh 100 nmol/min *v* control respectively) but not after (distal: 1.65 (0.37) *v* 1.63 (0.20) mm; proximal: 2.51 (0.57) *v* 2.51 (0.42) mm, both $p = NS$, ACh 100 nmol/min *v* control respectively) the LNMMA infusion. ACh caused a concentration dependent increase in CSO_2 both before the LNMMA infusion (60 (7) *v* 38 (8)% at 100 nmol/min, $p = 0.0007$) and after (57 (15)%, $p = 0.011$ compared with

control, $p = \text{NS}$ compared with ACh before the LNMMA infusion).

Inhibition of nitric oxide synthesis in the human coronary circulation caused a decrease in basal distal LAD diameter and basal coronary blood flow assessed by CSO_2 . Epicardial coronary artery dilatation in response to ACh is nitric oxide-dependent, but coronary resistive vessel dilatation is not.

Non-invasive detection of endothelial dysfunction in systemic arteries of children and adults at risk of atherosclerosis

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Endothelial dysfunction is an early event in atherogenesis and has been shown invasively in adults with established atherosclerosis. We have used high resolution ultrasound to study endothelial function in presymptomatic children and adults at risk of vascular disease. Superficial femoral artery (SFA) diameter and brachial artery (BA) diameter were measured at rest, during reactive hyperaemia (increased flow causing endothelium dependent dilatation), and after sublingual nitroglycerine (GTN, dilatation independent of endothelial function) in 100 patients; 50 controls aged eight to 57 (30 SFA, 20 BA), 20 smokers aged 30 to 52 (10 SFA, 10 BA), 10 children with hypercholesterolaemia aged eight to 16 (SFA) and 20 adults with coronary artery disease aged 54 to 67 (10 SFA, 10 BA). Blood flow velocity was measured at rest and during hyperaemia using Doppler. Images of sufficient quality for analysis were obtained in 94 cases (94%). In controls, there was an inverse relation between vessel diameter and flow mediated dilatation ($r = -0.81$, $p < 0.001$). In arteries ≤ 6 mm diameter, dilatation was 10 (2)%. By contrast, in smokers and children with hypercholesterolaemia, flow mediated dilatation was considerably reduced (SFA in hypercholesterolaemic children 0 (1)%, SFA in smokers 0 (1)%, BA in smokers 4 (2)%, all $p < 0.01$). Flow mediated dilatation was absent in 18 subjects with known coronary artery disease (0 (1)%, $p < 0.01$) (SFA eight, BA 10). Arterial dilatation to GTN was present in all groups (12 (1)%). The degree of reactive hyperaemia was comparable in all groups (350 to 800%), and results were reproducible in repeat studies performed in 21 subjects.

Endothelial dysfunction can thus be shown non-invasively in systemic arteries of young children and adults with risk factors for vascular disease, such as smoking and hypercholesterolaemia, before anatomical evidence of atherosclerosis. Serial study of vascular physiology will permit assessment of the impact of risk factor modification at an early stage of the disease process.

Coronary flow reserve is not impaired in syndrome X

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Several studies have reported a reduced coronary flow reserve in patients with chest pain, a positive exercise test, and angiographically normal coronary arteries (syndrome X). Different methods are available to measure coronary

flow reserve, but dipyridamole has consistently been the stimulus for eliciting coronary vasodilatation. We have evaluated coronary flow reserve in 19 patients by intracoronary papaverine, a well-established drug for this purpose. Epicardial coronary blood velocity was measured with an intracoronary Doppler flow probe and coronary artery diameter was determined by quantitative angiography. Estimates of coronary blood flow were made before and after intracoronary bolus injections of 8 mg papaverine in eight syndrome X patients and nine controls. The control group comprised patients with normal resting and exercise electrocardiograms and angiographically normal epicardial coronary arteries. No patient had features suggestive of hypertension, diabetes mellitus, left ventricular hypertrophy or cardiomyopathy. Coronary flow (the product of mean velocity and vessel area) was found before papaverine injection and at peak velocity change after injection. Coronary flow reserve (peak flow:baseline flow) was 3.97 (0.63) (mean (SEM) in syndrome and 4.05 (0.42) in control patients, ($p = 0.91$). With papaverine as the vasodilator agent coronary flow reserve is not impaired, in contrast to reports of reduced coronary flow reserve in syndrome X using dipyridamole.

Thus some of the manifestations of syndrome X may be due to an abnormality of the adenosine receptor.

Progressive intimal thickening after balloon angioplasty is related to rupture of the internal elastic lamina

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Intimal thickening, resulting from migration of smooth muscle cells from the tunica media and their proliferation, underlies the development of restenosis after balloon angioplasty. In this study we investigated the relation between the severity of the initial arterial injury and the extent of the subsequent intimal growth. Bilateral carotid angioplasty (five inflations; six atmospheres; 30 s duration; 60 s intervals) was performed in 12 pigs and the arteries were excised seven, 14, or 21 days (each, $n = 8$) later. After fixation, histological sections ($n = 6$) were taken at 0.5 cm intervals within the site of angioplasty and were stained with Van Gieson stain. The intimal area was measured by computerised planimetry. The depth of arterial injury in individual sections from each artery was defined as either deep (a tear through the internal elastic lamina into the media) or superficial (intact elastic lamina). The intimal area was comparable in sections showing either deep or superficial injury at seven days—(mean (SEM)) 0.223 (0.031) mm^2 v 0.113 (0.003) mm^2 respectively (NS), but was significantly greater in sections showing deep injury at both 14 days—0.385 (0.108) mm^2 v 0.110 (0.013) mm^2 ($p < 0.005$) and at 21 days—0.645 (0.083) mm^2 v 0.086 (0.020) mm^2 ($p = 0.0001$). Thus intimal area increased progressively with time in the presence of deep arterial injury (ANOVA $p < 0.005$), but was unchanged between seven and 21 days after superficial injury.

These results indicate that progressive intimal thickening after angioplasty occurs only when the internal elastic lamina is ruptured and suggest that the presence of an intact internal elastic lamina serves as a barrier to smooth muscle cell migration from the tunica media after balloon angioplasty.

Coronary endothelial and non-endothelial microvascular function are impaired in cardiac transplant patients early after operation

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Coronary occlusive disease after cardiac transplantation may be caused by perioperative factors damaging endothelial and vascular smooth muscle components of the coronary vasculature. Coronary flow measurements allow investigation of the vasodilatory responses of these elements of the coronary vascular bed. We investigated the hypothesis that coronary flow responses to papaverine (non-endothelial dependent vasodilator) and acetylcholine (endothelial dependent vasodilator) are impaired soon after cardiac transplantation. Fifteen transplant patients were studied three months after transplantation (group 1) and compared with 27 patients (group 2) without coronary occlusive disease on angiography (median four years after operation, range 2 to 8 years). A Doppler flow probe was inserted into the proximal left anterior descending coronary artery and incremental doses of intracoronary papaverine, and glyceryltrinitrate followed by acetylcholine were given until maximum hyperaemia was achieved. Coronary flow response was defined as the ratio of resting to peak coronary blood velocity. Coronary anatomy was assessed using quantitative coronary angiography. Coronary flow response to acetylcholine was lower in group 1 patients compared with group 2 patients—(mean (SD) 1.7 (0.8) *v* 2.7 (0.9), *p* = 0.003, Student's *t* test). Coronary flow response to papaverine was impaired in group 1 patients compared with group 2—3.2 (1.0) *v* 3.9 (1.0) (*p* = 0.04). Adjusting for the effect on endothelial dependent flow from non-endothelial dependent dilatation, there was a reduction in group 1 patients compared with group 2, but this did not reach conventional levels of statistical significance (coronary flow response to acetylcholine and papaverine was 58 (26)% *v* 70 (16)%, *p* = 0.09). No significant difference occurred in arterial diameter between groups after the vasodilatory drugs.

Impairment of endothelial and non-endothelial dependent microvascular vasodilation occurs soon after cardiac transplantation. This may contribute to the high early mortality in cardiac transplant recipients and may be related to the subsequent development of coronary occlusive disease.

Long-term outcome of adults with secundum atrial septal defect with and without surgical closure

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Eighty two patients with uncomplicated secundum atrial septal defect diagnosed in adult life (age 25 to 54, median 37) from 1955 onwards, were studied retrospectively. The aim of the study was to compare long-term outcome of patients who were operated on by surgical closure, with those who were not. Forty eight patients (age 26 to 51, median 36) had undergone surgical closure whereas thirty

four (age 25 to 54, median 38) did not. Mean Q_p/Q_s shunt ratios were 2.5:1 for those who were operated on compared with 2.4:1 for those who were not (NS) and mean pulmonary artery pressures were 30 (8) mm Hg and 26 (10) mm Hg in the surgical and medical groups respectively (NS). All patients were reviewed between March 1989 and February 1991. There were two cardiovascular deaths in those who were operated on and one in those who were not. After a mean follow up of 25 years from diagnosis, there was no difference in patient survival in between the two groups. New atrial fibrillation developed in 16 (33%) in the operated group and 12 (35%) in the non-operated group, making a total prevalence of 28 (58%) in those who had surgery, and 19 (56%) in those who did not. Neither the incidence nor the prevalence of atrial fibrillation was different between the two groups at the follow up. Need for diuretics was also similar in both the groups, 28 (58%) needed diuretics who had surgical closure and 15 (44%) who did not. In all patients who did not have surgical closure there was no clinical, radiological, and echocardiographic evidence of pulmonary arterial hypertension at the last follow up.

We conclude that surgical closure of secundum atrial septal defects in adults is not superior to medical management. Routine surgical closure of atrial septal defects in adults offers no advantage and is not justified.

Three and a half year review of paediatric heart and heart and lung transplantation

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From 176 patients assessed for transplantation between June 1988 and December 1991, 28 orthotopic heart transplants (3 weeks to 18 years, mean 11.0) and 23 heart and lung transplants (3 to 18 years, mean 11.4) were performed. The underlying diagnosis in the heart transplant group was cardiomyopathy (*n* = 13 (two were anthracycline induced)) and congenital heart disease (*n* = 15 including two with hypoplastic left heart syndrome). The heart and lung transplant group comprised cystic fibrosis (*n* = 19), Eisenmenger Syndrome (*n* = 3), and graft *v* host disease (*n* = 1). Donor selection was on ABO compatibility and body size with additional Cytomegalic antibody state matching in the heart and lung transplant group. Cyclosporine, azathioprine, and prednisone were used as immunosuppressive agents with delayed onset of steroids in the heart and lung transplant group. Antilymphocytic or thymocytic globulin and methyl prednisolone is used perioperatively. In the heart transplant group 20 patients survive all with an excellent quality of life, 3 to 36 months, mean 12; actuarial survival 69% at one and three years. All deaths occurred in the first two months, five from right ventricular failure within the first week. In the heart and lung transplant group 17 patients survive 2 to 42 months, mean 16.2; actuarial survival 74% at one year, and 65% at three years. Four of the deaths have been from obliterative bronchiolitis and three further patients have significant reduction in lung function from this disease. Fourteen patients currently have a good quality of life.

Can the transplanted heart grow in children? An investigation of insulin-like growth factor gene expression

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It is fundamental for the success of the worldwide paediatric cardiac transplantation programme that the transplanted heart can grow. Therefore we have investigated expression of insulin like growth factor 1 (IGF-I), a major mediator of growth, in right ventricular endomyocardial biopsy specimens from 14 children (age range 10 to 19 years, median 15, donor age 6 to 41 years, median 19), and 10 adult recipients (48 to 59 years, median 53). Extracted ribonucleic acid (RNA) was hybridised to an IGF-I c deoxyribonucleic acid using slot and northern blot analysis. A mRNA transcript of 4 kilobases was present in the paediatric population but was absent in the 10 adults. Using radioimmunoassay, IGF-I was detected in all specimens (100 (46) pg/mg soluble protein, in the paediatric group and 16 (8) pg/mg soluble protein in the adult group), concentrations were significantly higher ($p < 0.001$) in the paediatric patients in whom there was also a correlation with densitometric readings of slot blot autoradiograms for IGF-I mRNA ($p < 0.001$ $r = 0.7$). Plasma IGF-I concentrations were within expected normal ranges in all patients, mean 164 (9) ng/ml and 176 (17) ng/ml for the paediatric and adult groups respectively.

Gene expression of IGF-I mRNA in the myocardium in young transplant recipients is reassuring evidence for preservation of the molecular basis for cardiac growth.

Response to dynamic exercise after paediatric cardiac transplantation

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To assess exercise performance after paediatric heart transplantation, 18 children (11 male), surviving 0.5 to 5.4 years (mean 1.9) after transplantation underwent bicycle ergometry with a continuous graded protocol (Godfrey 1974). All were in New York Heart Association class I. Results were compared with those from 18 age and sex matched controls (Student's t test). Parameters measured included: heart rate, O_2 consumption/kg, expired CO_2 , minute ventilation, work rate and endurance time. Results for peak exercise are shown as mean (SD), and peak heart rate, O_2 consumption and work rate are also expressed as % of peak predicted values based on established "normal" data: Patients and controls were well matched for age (13.7 (3) years, controls 13.8 (2.2); $p > 0.1$), and weight (48.6 (19.8), controls 58.2 (17.9); $p > 0.1$). All other parameters differed significantly between the two groups. Patients v control, heart rate 145 (27) v 195 (12) ($p = 0.0001$); O_2 consumption (ml/kg/min) 25.6 (6.9) v 41.2 (9.5) ($p = 0.0001$); work rate (watts) 85 (41.1) v 181 (58.4) ($p = 0.0001$); ventilation (l/min) 57.8 (21.9) v 91.5 (31.1) ($p = 0.0017$); expired CO_2/O_2 consumption 1.23 (0.08) v 1.12 (0.09) ($p = 0.0015$); endurance time (mins) 6.5 (1.9) v

10.7 (2.3) ($p = 0.0001$). Per cent predicted peak values (patients v control) were: heart rate 70.7 (13.4) v 94.6 (5.6); O_2 consumption 61.6 (11.7) v 92.3 (16.5); and work rate 59.8 (15.1) v 109.6 (18). No correlation was seen between these three parameters and time from transplantation ($r = -0.24$ to $+0.08$; all $p > 0.4$). Impaired exercise performance was seen in the absence of anaemia or chronic steroid usage, and in those who subjectively were of above average fitness.

Peak work rate, O_2 consumption, and heart rate are significantly reduced in asymptomatic transplanted patients and may not improve with time. Chronotropic incompetence is a likely major factor limiting exercise performance, but others, such as poor conditioning, may contribute. Longitudinal studies are required to better define those factors that limit exercise performance in this group of patients.

Pulmonary hypertensive crisis in infancy treated with extracorporeal membrane oxygenation

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Extracorporeal membrane oxygenation (ECMO) is a process of life support developed from modifications in heart lung bypass technology. It has achieved most success in the treatment of neonatal pulmonary failure but has also proved successful in the management of cardiopulmonary or cardiac failure. The ECMO service in Leicester commenced in 1988 and so far a total of 37 patients have been treated: 24 neonates, 10 paediatric patients, and three adults. From this series we present 11 infants with pulmonary hypertension treated with ECMO. Eight of these patients were neonates with persistent foetal circulation, one patient had total anomalous pulmonary venous return, one patient had functional pulmonary atresia, and one patient had a pulmonary hypertensive crisis after surgical repair of truncus arteriosus. In the absence of anatomical abnormality a survival rate of 63% was achieved in the patients with persistent foetal circulation. All the other patients presented survived. The total duration of bypass required varied from 36 to 222 hours (mean 116). All the patients with an anatomical cause for pulmonary hypertension were treated with venoarterial perfusion (cardiopulmonary support). Those with persistent foetal circulation were treated either with venoarterial or venovenous (pulmonary) support. Candidates eligible for ECMO are restricted by size and maturity (2 kg and 34 weeks completed gestation). They must not have had pre-existent intracranial haemorrhage and must have been ventilated for less than seven days. ECMO for cardiopulmonary support in cardiac patients can be used pre, peri, or post-operatively and the worldwide average survival rate is 50%. Success when used as a means to support patients who cannot be weaned from operative cardiopulmonary bypass is limited to 5%, however. Selection of patients for ECMO support is based upon the potential reversibility of the primary pathology and a failure to respond to maximal conventional medical treatment. Numerical criteria are available to assist in cases of persistent foetal circulation.

We have found this technique effective in a variety of circumstances and would advocate its use in acute pulmonary hypertension resistant to other forms of treatment.

Role of pulmonary valve insertion in reoperation for progressive late right ventricular dysfunction after repair of tetralogy of Fallot

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Clinical, echocardiographic, and radioisotope methods were used to assess the clinical outcome and right ventricular performance after pulmonary valve insertion for late right ventricular dysfunction after intracardiac repair of tetralogy of Fallot. From 1975 to 1990, 129 patients underwent successful intracardiac repair of tetralogy of Fallot. Although initially asymptomatic, 10 (7.8%) of these patients developed evidence of late right ventricular dysfunction with severe pulmonary and tricuspid insufficiency. In this subgroup, the mean age at intracardiac repair was 3.7 years and all patients had a pericardial transannular patch, extending to pulmonary branch patch angioplasty in two cases. The mean interval from intracardiac repair to reoperation was 6.2 years. No patient had a residual ventricular septal defect or right ventricular outflow tract gradient, but eight patients showed abnormalities of pulmonary arterial system (pulmonary artery branch stenosis in six, abnormal peripheral pulmonary arteries in five, systemic collateral arteries in three). Tissue valves were initially inserted in all patients with no operative deaths. Late follow up extends to 11 years (mean 7.3 years). There have been no late deaths. Three patients have required a total of four further reoperations for valve dysfunction. All achieved long term clinical improvement (New York Heart Association class I or II). Six patients underwent rest and exercise radionuclide (intravenous xenon-133) and echocardiographic study (mean 6.7 years) after pulmonary valve insertion, which confirmed preserved right ventricular function with good exercise tolerance (significant reduction of right ventricular dilatation, mean right ventricular rest ejection fraction 0.51 with >5% increase with exercise).

These results suggest that pulmonary valve insertion with transannular patch reconstruction for progressive late right ventricular dysfunction after intracardiac repair of tetralogy of Fallot can be accomplished with low operative risk and good early haemodynamic and clinical results. The progress of right ventricular dysfunction appears to be halted or at least substantially delayed by this approach although long-term review is indicated.

Determinants of myocardial revascularisation in patients with coronary artery disease: a report from the RITA coronary arteriogram register

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The multicentre RITA trial coronary arteriogram register (1988–90) has been analysed to determine factors influencing the use of myocardial revascularisation procedures (coronary bypass surgery or coronary angioplasty). Of 23 968 patients with coronary artery disease 64% were referred for revascularisation, but this varied from 48% to 83% between centres. Multivariate analysis (multiple logistic regression) identified the extent of coronary dis-

ease, the number of anti-anginal drugs, catheterisation for angina, left ventricular function, and diuretic treatment (but not age or gender) as important independent determinants of revascularisation. Adjustment for these variables did not account for the between centre differences, and after multivariate analysis the odds of revascularisation at the centre with the highest intervention rate were increased by factor of 4.2, relative to the centre with the lowest intervention rate. In a separate analysis of 14 622 patients referred for a revascularisation procedure the likelihood of surgical intervention (as opposed to coronary angioplasty) was independently influenced by age, left ventricular function, the extent of coronary disease, and the participating centre. After multivariate analysis the odds of surgery at the centre with the highest surgical referral rate were increased by a factor of 5.7, relative to the centre with the lowest referral rate.

These data show important differences between centres in the use of myocardial revascularisation procedures, which could not be explained by between centre variation in their patients.

Intravenous anistreplase in acute myocardial infarction: continued reduction in mortality up to five years: long-term results of the APSAC International Mortality Study (AIMS)

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The APSAC Intervention Mortality Study (AIMS) reported a reduction in mortality maintained for one year. Long-term follow up has been continued up to 5.5 years from randomisation of the first patient. A total of 1258 of 1264 entered patients were randomised using a double blind placebo controlled design within six hours of symptoms with electrocardiographic evidence of infarction, to either 30 U intravenous anistreplase (A) or placebo (P). Heparin was introduced six hours after treatment, oral warfarin was continued for at least three months. Timolol, where appropriate, was given for up to one year. Follow up was maintained by "flagging" patients with the help of the Office of Population Census and Surveys. Data were analysed using lifetable analysis. Results are reported as odds reduction of death (OR) with 95% CI. At 30 days 6.4% of patients died after A compared with 12.1% after P (OR 50.5% (26.1–66.8%)). At one year for 624 patients in the A group, 11.2% died compared with 17.9% in the P group (OR 41.8% (19.8–57.8%)). In years 2 and 3 after therapy, estimated mortality still showed a reduction (14.3% A *v* 19.1% P (OR 29.4% (4.6–47.8%) year 2) and 15.7% A *v* 21.3% P (OR 30.8% (7.4–48.2%) year 3). In year 4, 155 A and 154 P patients were censored. Estimated mortality was 17% in A patients compared with 22.9% in P patients (OR 30.9% (8.3–47.9%)). In year 5, mortality estimates were 19.3% in A patients and 24% in P patients (OR 25.2% (1.3–43.3%)).

These results confirm that the reduction in mortality seen in the AIMS study after anistreplase in acute myocardial infarction previously reported at 30 days and one year is maintained for up to five years.

Reduced in-hospital mortality from acute myocardial infarction in the North West Thames Regional Health Authority (1980–89) with general adoption of fibrinolytic therapy

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Fibrinolytic therapy substantially reduces mortality due to acute myocardial infarction. This study assesses the impact of the introduction of this treatment on in-patient mortality during the decade 1980–89. An estimate of the number of lives saved in 1989 attributable to use of fibrinolysis was made. Figures for annual admissions and deaths due to acute myocardial infarction were obtained in the North West Thames Regional Health Authority which serves a population of 3.5 million. Between 1987 and 1990, annual usage of fibrinolytics has increased by 81%, from 1697 doses to 3066 doses. Currently fibrinolysis is given to about 50% of patients with acute myocardial infarction. During the decade, 48 861 patients, (31 868, 65% male) were admitted with acute myocardial infarction. Numbers of cases and mortality increased sharply with age. Between 1980 and 1986 mortality of acute myocardial infarction was stable at about 27%. Over the whole period however, total acute myocardial infarction mortality declined by 19% from 27% in 1980 to 21.9% in 1989 ($p < 0.0001$). Mortality fell from 6.5% to 2.6% of those aged < 45 ($p < 0.0001$) (10 lives saved), 14.5% to 8.6% of those aged 45–64 ($p < 0.0001$) (89 lives saved), 29.6% to 18.4% of those aged 65–74 ($p < 0.0001$) (138 lives saved), and from 49.9% to 39.2% of those aged > 74 years ($p < 0.0001$) (168 lives saved). Overall mortality in men fell by 22% from 22.6% to 17.5% ($p < 0.0001$) (248 lives saved). Overall mortality in women fell by 18% from 36.4% to 29.9% ($p < 0.0001$) (156 lives saved). Extrapolated to the national population about 5800 lives per year are being saved in England and Wales.

Increased use of fibrinolysis has resulted in important reductions in mortality especially in younger patients, and there is further scope for its use particularly in the elderly.

Results of HAL-1 (Heart Attacks in London) study: potential for earlier treatment by prehospital initiation of fibrinolytic therapy

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We investigated the potential time to be gained by prehospital treatment with fibrinolysis in London. Over a three month period London Ambulance Service crews filled in a questionnaire in cases of suspected acute myocardial infarction. One thousand two hundred forms were returned; 780 patients (65%) were men: mean age was 66 (16); 156 (13%) required immediate cardiopulmonary resuscitation. In the remainder, symptomatic data were available in 934. The major symptom was severe chest pain in 394 (42%); 257 (28%) had severe chest tightness; 158 (17%) had severe pressure in the chest. The remainder, 125 (13%) had severe dyspnoea. In 97 (10%) cases a doctor was present at the time of ambulance arrival. Exact information on time of onset of symptoms was available in 887. In these cases, 466 (52%) calls were made within the first hour from onset of symptoms, mean 21 (17) min. For this

group, the mean time from onset of symptoms to the arrival of the ambulance was 31 (19) min. The mean time from ambulance arrival to arrival at hospital was 25 (10) min. The mean time from onset of symptoms to hospital arrival was 56 (22) min. In this subgroup of patients calling within one hour of the onset of symptoms, 41 (89%) were seen by an ambulance crew within an hour from the onset of symptoms whereas only 285 (61%) arrived at a hospital within this time. Recent studies have shown delays of 30 min following hospital arrival before fibrinolysis is administered.

In London, initiation of thrombolysis by trained ambulance personnel could save about 60 min in those patients calling the ambulance service within one hour of the onset of symptoms.

Thrombolytic therapy in acute infarction: circadian variations in the onset of symptoms and silent ischaemia during early recovery

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Circadian variations have an important effect on the timing of acute ischaemic syndromes and have also been shown in patients with silent ischaemia. There is, however, no information about circadian influences on the timing of silent ischaemia in the early recovery period after acute myocardial infarction although it may be an important risk factor for recurrent ischaemic events, particularly in patients treated by thrombolysis. We have recorded the time of onset of chest pain in 598 patients with acute myocardial infarction and confirmed a highly significant circadian variation peaking in the early waking hours (06.00 to 10.00 hours) with a secondary evening peak at 20.00 hours ($p < 0.01$). The circadian rhythm was independent of age, sex, smoking, hypertension, diabetes, and racial group. One hundred and forty patients, all of whom had been treated by thrombolysis, underwent 48 hour Holter ST monitoring two days later when all symptoms had resolved. Silent ischaemia was documented in 53 patients, as evidenced by either > 0.2 mV ST elevation or > 0.1 mV ST depression. Circadian variations in the duration of silent ischaemia were closely similar to the variations in the onset of chest pain documented in the acute phase of infarction, with morning and evening peaks at the same times.

Circadian variations in the onset of chest pain in acute myocardial infarction also have a role in the early recovery period after thrombolytic therapy, as evidenced by the timing of silent ischaemia during Holter monitoring. The data suggest that the same circadian mechanisms predisposing to coronary thrombosis in acute infarction continue to operate early after thrombolytic therapy when the patient remains at risk of recurrent ischaemic events.

Effect of late thrombolysis on left ventricular remodelling and function after myocardial infarction

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Late thrombolysis lessens mortality after acute myocardial infarction possibly by limiting left ventricular dilatation.

To examine the changes in left ventricular function and volume occurring after acute myocardial infarction, 50 consecutive patients receiving thrombolysis for a first acute myocardial infarction were studied by gated radionuclide ventriculography within 5 (3) and 56 (10) days of presentation. Left ventricular ejection fraction (LVEF) and left ventricular volume were measured; the second by a non-geometric method but without correction for attenuation. Group A (n = 20) and group B (N = 30) received thrombolysis within three hours and 4 to 24 hours of symptom onset respectively. Coronary angiography was performed at six weeks and patency of the infarct related artery (IRA) assessed. In 16/20 (80%) group A and 21/30 (70%) group B patency of the IRA was evident. Initial end diastolic volume index (EDVI) for groups A and B was similar (19.4 (6.7) ml/m² v 20.2 (7.4) ml/mm² NS), however, eight week EDVI for group A was smaller than for group B (20.6 (6.5) ml/m² v 27.6 (10.9) ml/m², p < 0.01). Left ventricular dilatation (>20% increase in volume) developed in 28 patients. Amongst group A patients with a patent IRA left ventricular dilatation occurred in only 4/16 (25%); in 12/16 (75%) patients left ventricular volumes remained stable or diminished. Two out of four group A patients (50%) with an occluded IRA exhibited left ventricular dilatation; no alteration in volume was noted in the other 2/4 (50%) patients. Among group B patients with a patent IRA left ventricular dilatation occurred in 15/21 (71%) patients; in 6/21 (29%) patients left ventricular volumes did not alter; 7/9 (77%) group B patients with an occluded IRA exhibited left ventricular dilatation; in 2/9 (23%) patients left ventricular volumes remained stable. LVEF increased significantly with time only among group A patients with a patent IRA (58.7% (16.0%) v 66.6% (10.6%), p < 0.05).

These data indicate that early thrombolysis achieves vessel patency and limits left ventricular dilatation. Late thrombolysis, although successfully achieving vessel patency, fails to limit left ventricular dilatation after infarction. Only patients in whom reperfusion is successful early exhibit improved systolic function with time after infarction.

Temporary pacing: continuing failures in general medical management

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Temporary pacemaker insertion is a commonly performed practical procedure and has been shown to have a high associated morbidity. To assess current practice we prospectively monitored complications of temporary pacing in 40 patients referred over an eight month period from district general hospitals to a regional centre for permanent pacing. In 52.5% of cases (21/40) temporary pacemaker related complications were present and in 20% (8/40) dual problems were encountered. The indication for temporary pacing was considered spurious in 7.5% (3/40). Complete or intermittent non-capture of the ventricle was 10% of cases (4/40). The temporary pacemaker was malpositioned in 20% (8/40) of patients and in two of these was located in the pericardium, with associated diaphragmatic pacing in one case. A pneumothorax was present in 5% (2/40) cases. Eight patients (20%) had an infected temporary pacemaker on arrival at the regional centre. The mean duration of temporary pacing before transfer was increased in infected pacemakers (infected mean 8.0 days, non-infected mean

6.3 days, p = 0.086), and the presence of complications was associated with an increased inpatient stay at the regional centre (uncomplicated mean 3.65 days, complicated mean 8.0 days, p < 0.01). The relative experience of the 12 referring hospitals was not a factor in their individual complication rate.

Temporary cardiac pacing continues to be performed poorly and remains a cause of significant morbidity and expense. An improvement in practice will only come from improved training and supervision of junior physicians, and early transfer to a regional centre.

Chronic sensing thresholds during sinus rhythm and tachycardia: implications for pacing

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It is important that intracardiac electrograms are appropriately sensed during both sinus rhythm and tachycardia by an antitachycardia pacemaker or defibrillator so that treatment is delivered only when appropriate and not withheld during an arrhythmia. Atrial sensing thresholds during sinus rhythm and supraventricular tachycardia was measured in 28 patients with implanted pacemakers (intermedics Intertach 262-12 in 17 (group 1) and -16 in 11 (group 2)). Measurements during both sinus rhythm and tachycardia are available in 8/17 group 1 patients and in 8/11 group 2 patients. There was no significant difference in sensing threshold during sinus rhythm and supraventricular tachycardia in either group (group 1 1.8 (0.1) v 1.7 (0.3), group 2 2.6 (0.3) v 2.3 (0.3) mV, NS). In individual patients, however, the threshold fell during supraventricular tachycardia compared with sinus rhythm in 6/16 (37%: 3 in group 1 and 3 in group 2), remained the same in six (37%: 3 in group 1 and 3 in group 2), and rose in four (25%: 2 in group 1 and 2 in group 2). The change in threshold was ≥ 2 points on the available scale in 8/16 (50%). Measurements were made on more than two occasions in 10 patients. There was no significant difference in either absolute thresholds or in changes between sinus rhythm and supraventricular tachycardia.

Sensing threshold during supraventricular tachycardia cannot therefore be assumed from the sensing threshold during sinus rhythm. The threshold during tachycardia may be either higher or lower than that in the sinus rhythm. This may lead to either failure to detect tachycardia or to inappropriate sensing and pacing during sinus rhythm with induction of tachycardia.

An assessment of changes in cardiac responses to activities of daily living in pacemaker patients using a new ambulatory nuclear vest: comparison of WI and DDD pacing

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A new non-imaging ambulatory nuclear device (Capintec vest), using a single crystal probe, was used to measure changes in ejection fraction (EF) and cardiac output (CO) in six men who each had a DDD pacemaker for complete heart block. This device continuously measures changes in cardiac responses at rest and during activities of daily living such as walking and climbing stairs. Each patient underwent a conventional multigated acquisition scan to calcu-

late resting EF. The probe was positioned over the blood pool in the left ventricle using the gamma camera and securely fastened with a plastic vest. Patients then underwent a protocol which included a 10 min corridor walk, climbing a flight of stairs, and a symptom limited exercise test (bicycle ergometer) with rest periods. The pacing mode was switched from VVI to DDD in a parallel group crossover design. The patients (age range 60–68) had been paced for six months and had normal left ventricular function (EF 50–55%). The atrioventricular delay had been individualised between 200–225 msec and upper rate response at 135–140 beats per min. Bicycle exercise duration was 10–14 min. The mean percentage change in EF and relative CO respectively from VVI to DDD were: resting mode 11% and 9%; corridor walk 13% and 12.5%; climbing stair 11% and 14%; exercise 14% and 15%.

The study suggests that this new ambulatory nuclear device can be used for assessing patients with permanent pacemakers; EF and CO are higher with DDD pacing at rest, during exercise testing, and also during activities of daily living.

Is the pacemaker syndrome caused by increased variability of pulmonary venous blood flow?

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Variation in pulmonary venous blood flow during single and dual chamber pacing was assessed using transoesophageal echocardiography and related to pacing mode preference during everyday activity. Ten patients randomly paced in VVIR, DDIR, and DDDR modes were subjectively assessed by validated questionnaires after four weeks outpatient activity. All then underwent transthoracic Doppler-echocardiography (assessing stroke volume, cardiac output, extent of tricuspid and mitral regurgitation, and bloodflow in the superior vena cava). This was followed immediately by transoesophageal echocardiography to assess pulmonary venous blood flow in VVI and DDD modes at rest and paced at 85 beats per min in a double blind crossover design. Seven patients (70%) preferred DDDR and found VVIR least acceptable with three (30%) suffering overt pacemaker syndrome and demanding early mode change, forming the (PS) group. One patient preferred VVIR and two (20%) had no preference and these formed the "tolerated VVIR" (TV) group. The remaining four patients formed the "preferred DDDR" (PD) group. Transthoracic Doppler echocardiography derived stroke volume was greater in DDD than VVI modes ($p < 0.04$) in the PS group at rest but not in either PB or TV groups (NS). Cardiac output, mitral, and tricuspid regurgitation, and variability of superior vena cava blood flow at rest and 85 beats per min in VVI and DDD modes did not differ in any group. Variability of the transoesophageal Doppler echocardiography derived pulmonary venous blood flow forward velocity integral was significantly greater, however, during VVI than DDD pacing at rest in both PS and PD groups ($p < 0.05$) but not in the TV group. Pulmonary venous blood flow reversal variability during atrial systole was significantly greater in VVI in all groups ($p < 0.01$) but did not predict mode preference.

These results suggest that left atrial receptors may be triggered by increased pulmonary venous bloodflow variability including adverse circulatory responses resulting in the pacemaker syndrome.

Beat to beat variability of stroke volume during VVI pacing as predictor of haemodynamic benefit from DDD pacing

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Asynchronous atrial contraction during VVI pacing may result in greater beat to beat variability of stroke volume compared with DDD pacing. To determine whether beat to beat variability of stroke volume during VVI pacing can predict haemodynamic benefit from DDD pacing, we undertook Doppler recordings of aortic and mitral flow during both DDD and VVI pacing in 15 pacemaker dependent patients with DDD pacemakers (mean age 49 (21), range 17–70). Heart rate was kept at 70 bpm during pacing at both modes and the atrioventricular delay was set at 150 ms during DDD pacing. Left ventricular systolic function was good in all patients. Seven patients had a history of myocardial infarction and a reduced ratio of early (E) to late (A) transmitral flow velocities during DDD pacing (mean E/A 0.6 (0.2)). Eight patients had a normal E/A (mean 1.6 (0.5)). Beat to beat variability of stroke volume was defined as the standard deviation/mean value of the time velocity integral of aortic flow over 10 beats, expressed as %. Stroke volume increased by 26 (16)% from VVI to DDD ($p < 0.01$). This increase was greater in patients with reduced E/A (35 (10)% increase) compared with patients with normal E/A (16 (10)% increase; $p < 0.05$). Beat to beat variability of stroke volume was greater in VVI mode (14 (9)%) compared with DDD (4 (1)%) ($p < 0.01$). Patients with reduced E/A showed greater beat to beat variability of stroke volume during VVI pacing (20 (6)%) compared with patients with normal E/A (6(2)%) ($p < 0.01$).

Patients who derive most haemodynamic benefit from DDD pacing are those with reduced E/A and they show greater beat to beat variability in stroke volume during VVI pacing. High beat to beat variability of stroke volume during temporary VVI pacing before permanent implantation may identify patients likely to benefit from DDD mode, enabling cost effective use of modern pacemaker technology.

Long-term results of antitachycardia pacing for supraventricular tachycardia

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The long-term efficacy of antitachycardia pacing for supraventricular tachycardia is not known. Atrial fibrillation is a potential complication. The outcome has been reviewed in 101 patients with supraventricular tachycardia treated in nine centres with Intertach pacemakers. Twenty two per cent were men; mean age was 44.8 (range 16 to 84); 72 had been in hospital 3.1 (1 to 31) times with supraventricular tachycardia; 92 had unsuccessfully used four (1 to 11) drugs; 73 had atrioventricular node reentry; 23 had accessory pathways, concealed in 11, overt in 10. Complications included venous thrombosis in five, infection in five, lead displacement in two, and other problems requiring surgery in seven. During follow up of 32.4 (2 to 72) months all 101 have functioned appropriately. One patient was lost to fol-

low up at 15 months. Ten pacemakers have been explanted (six at accessory pathway surgery, two at atrioventricular node ablation, two for infection). Two are inactive (one atrial fibrillation, one accessory pathway). Explanation rates per centre varied from 0/25 to 2/4 (0–50%). One (1%) patient has chronic atrial fibrillation (at three years), and 12% have had transient atrial fibrillation. This was not related either to age or to an accessory pathway. Six of 26 (23%) followed up for > 4 years have had atrial fibrillation, as has one of 11 (10%) followed up for > 5 years; 16% have been in hospital with supraventricular tachycardia or atrial fibrillation after implantation; 24% take antiarrhythmic drugs; and 18% β blockers.

Thus antitachycardia pacing was effective in a large series of patients with supraventricular tachycardia, particularly those with atrioventricular node reentry, reducing the need for admission to hospital and for antiarrhythmic drugs. Chronic atrial fibrillation was rare in this population.

Monocytes inhibit intimal smooth muscle proliferation: in vitro studies with human saphenous vein

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An in vitro coculture system was established to investigate the hypothesis that human monocytes and low density lipoprotein (LDL) influence the development of intimal hyperplasia in human saphenous vein. Vein segments obtained from patients undergoing coronary artery bypass surgery were opened out and 6 mm diameter discs were cut using the blade of a corneal trephine. Discs were cultured for eight days in 1.5 ml of RPMI medium containing 30% (v/v) foetal bovine serum with or without 1 mg/ml human low density lipoprotein. The medium was changed every two days and was supplemented with 1 μ Ci/ml of (3 H) thymidine for the last 24 hours. Monocytes were obtained 95% pure from the blood of healthy volunteers using density gradient centrifugation and $0.2\text{--}1.0 \times 10^6$ of freshly isolated monocytes were added to the veins on the second day of culture. Transverse paraffin sections (5 μ m) were used to quantify ((a) monocytes stained using the monoclonal antibody HAM 56, (b) intimal thickness, and (c) (3 H) thymidine labelled (proliferating) cells. The number of monocytes/mm length detected in the intima of the veins was (mean (SE)) 0.2 (0.1), 1.5 (0.7)*, 2.2 (1.2), and 3.3 (0.7)* when 0, 0.2, 0.5, and 1.0×10^6 monocytes were added to the cultures ($n \geq 8$, * $p < 0.05$ v addition of no monocytes). The corresponding intimal thicknesses were 16 (2), 12 (3), 6 (2)* and 8 (2) μ m*. The corresponding numbers of (3 H) thymidine labelled cells were 5.3 (0.9), 2.6 (0.7), 2.1 (0.7)* and 2.1 (0.6)*. Adding 1 mg/ml human LDL to cultures ($n = 7$) throughout the culture period did not alter any of these values either in the presence or absence of monocytes (data not shown). The results show that monocytes migrated into the intima of human saphenous vein and inhibited intimal proliferation.

Attenuation of smooth muscle proliferation has been postulated as an underlying cause of plaque rupture, which occurs in atherosclerotic arteries in areas of highest macrophage density. Our results imply that monocytes directly inhibit smooth muscle proliferation. This in vitro model may be used further to provide an insight into the mechanisms involved.

Role of c-myc proto-oncogene expression in inhibition of vascular smooth muscle cell proliferation

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Proliferation of vascular smooth muscle cells (VSMC) contributes to angioplasty restenosis, vein graft occlusion, and atheroma formation and may be amenable to pharmacological intervention. An early response to inhibition of cellular proliferation is decreased expression of the growth-regulatory proto-oncogene c-myc. Conversely, in human atheroma VSMC proliferation, overexpression of c-myc has been described, implying that this may be part of the pathogenic mechanism. To further define the role of c-myc in inhibition of VSMC proliferation, we studied changes in c-myc expression in rat aortic VSMC during logarithmic growth in 10% serum medium and during growth arrest in response to heparin (50 μ g/ml), the cyclic nucleotide analogues, 8-Br-cAMP (0.1 mM), 8-Br-cGMP (0.1 mM), and transfer to 0.5%-serum medium. Expression of nuclear c-myc protein was localised by indirect immunofluorescence confocal microscopy and was quantified in 20 cells per condition using image analysis. C-myc RNA expression was measured by northern analysis, and proliferation by cell counting. Culture in 0.5%-serum led to a fall in c-myc oncoprotein expression from 24 (5) (SD) to 5 (1) fluorescence units at two hours ($n = 4$, $p < 0.001$ v 10% serum) and inhibited proliferation from $1.6 (0.2)$ to $0.20 (0.04) \times 10^5$ cells at 48 hours ($n = 3$, $p < 0.001$). Heparin, 8-Br-cAMP, or 8-Br-cGMP did not reduce c-myc expression at two hours (26 (2), 28 (4), 29 (3), respectively $n = 4$) or at 24 hours (not shown), despite significantly inhibiting proliferation to $0.95 (0.11)$, $0.77 (0.15)$ or $0.83 (0.12) \times 10^5$ cells respectively ($n = 4$, all $p < 0.05$ v 10%-serum). Expression of c-myc RNA was also decreased by > 90% after two hours of 0.5%-serum culture. Flow cytometric analysis confirmed that both 0.5%-serum and the pharmacological inhibitors arrested cells in the G1 phase of the cell cycle.

The data show that reduction of serum concentration led to an early decrease in expression of c-myc protein and RNA, whereas the pharmacological inhibitors did not. They therefore distinguish at least two pathways of growth inhibition of VSMC proliferation, both of which merit further investigation.

Effect of ramipril on the response to vascular injury induced by balloon catheter in the rat

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Balloon angioplasty of the coronary arteries produces endothelial denudation and disruption of the atherosclerotic plaque and damages the media of the artery. During repair of the vessel wall, medial smooth muscle cells proliferate and migrate to form fibrocellular intimal hyperplasia, which, where excessive, leads to restenosis. We examined the effect of different doses of ramipril, an angiotensin converting enzyme inhibitor that has high affinity for tissue angiotensin converting enzyme, on fibrocellular intimal hyperplasia after injury induced by balloon cath-

eter in the carotid artery of the rat. Male Wistar rats (body weight 300–350 g) received normal drinking water (A, $n = 13$) or water containing ramipril (B, 0.1 mg/kg/day, $n = 15$; C, 1 mg/kg/day, $n = 15$; D, 10 mg/kg/day, $n = 14$) starting three days before left common carotid injury with an FG2 Fogarty balloon catheter. The animals continued to receive the drug or normal water for 14 days after the vessel injury at which time the rats were anaesthetised, exsanguinated, then perfused fixed with 2% glutaraldehyde and 1% formaldehyde at 120 mm Hg perfusion pressure. Left and right carotid arteries were isolated and placed in fixative for a further 24 hr then embedded in araldite. Semi-thin sections were stained with toluidine blue and evaluated morphometrically using a context vision image analysis system. Results were analysed by an analysis of variance. Plasma angiotensin converting enzyme activity was reduced significantly ($p < 0.05$) in a dose-dependent manner (A 171 (29), B 117 (18), C 100 (15), D 52 (7) U/L (mean (SEM)). A single layer of endothelial cells formed the intima of the right carotid artery. That of the injured left carotid artery was greatly thickened by smooth muscle cells and connective tissue. The cross sectional area of neointima was 0.158 (0.022) mm² in untreated animals (A) but was reduced at doses of ramipril > 0.1 mg/kg/day (B 0.133 (0.018) mm² (NS); C 0.076 (0.014) mm² ($p < 0.001$); D 0.072 (0.013) mm² ($p < 0.001$). These data show that ramipril reduces fibrocellular intimal hyperplasia in a dose dependent manner after balloon catheter injury in the rat.

The data support the suggestion that angiotensin converting enzyme inhibition may be useful in preventing restenosis after coronary angioplasty.

Platelet adhesion after balloon angioplasty is inhibited by SIN-1 an exogenous donor of nitric oxide

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Platelet adhesion contributes to acute thrombus formation and intimal hyperplasia after balloon angioplasty. Endogenous nitric oxide (NO), endothelium-derived relaxing factor, inhibits platelet adhesion in vitro. We investigated whether SIN-1, an exogenous source of NO, inhibits platelet adhesion in vivo after bilateral carotid angioplasty in heparinised pigs. SIN-1 (intravenous; 10 µg/kg/min; $n = 6$) or placebo ($n = 6$) were given before and during the angioplasty procedure. Platelet deposition was quantified by autologous ¹¹¹indium labelled platelets. The depth of arterial injury, determined histologically, was defined as superficial (endothelial denudation) or deep (rupture of the internal elastic lamina). Artery samples were taken for scanning electron microscopy. SIN-1 prolonged the bleeding time (mean (SE)) 56 (12)% *v* 4 (4)% ($p < 0.01$) and raised platelet cyclic GMP 96 (36)% *v* 4 (14)% ($p < 0.05$). SIN-1 significantly inhibited platelet deposition on segments with superficial injury (platelets $\times 10^6$ /cm²) 1.92 (0.57) *v* 5.54 (0.71) ($p < 0.005$) and deep injury 6.66 (2.12) *v* 27.32 (7.56) ($p < 0.05$), without affecting it on

distal uninjured segments—0.18 (0.05) *v* 0.27 (0.08) ($p = \text{NS}$). Scanning electron microscopy confirmed that SIN-1 reduced the platelet monolayer adherent to areas of endothelial denudation.

These data provide the first evidence that nitric oxide inhibits platelet adhesion in vivo. The results also indicate important therapeutic potential for SIN-1 as an agent which may influence the pathophysiological response to vessel wall injury.

Human recombinant tissue-type plasminogen activator enhances wound healing in human coronary artery endothelial cells

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Endothelial cell migration is essential to angiogenesis and the repair of breached endothelium. Tissue plasminogen activator (tPA), synthesised by endothelial cells, converts plasminogen to plasmin that disrupts the basement membrane, facilitating endothelial cell migration. Tissue plasminogen activator alone promotes migration in endothelial cells of the umbilical vein. Endothelial cells of different origins, however, exhibit functional heterogeneity. We have therefore investigated the effect of tPA on migration in a novel human coronary artery endothelial cell system. The system is serum free, permitting investigation of tPA in the absence of plasminogen. Normal coronary artery and aortic endothelial cells were isolated by collagenase digestion of surgical specimens and cultured. Confluent cells were passaged onto fibronectin coated Thermanox coverslips and characterised as endothelial by their cobblestone morphology, and granular pattern of von Willebrand factor immunoreactivity. The monolayer was wounded with a 1.4 mm resin scraper and washed in serum free medium (with 0.5% bovine serum albumin, 0.2% gelatin) to remove serum and detached cells. During 30 hours incubation in serum free medium containing human recombinant tPA (rtPA, Boehringer Ingelheim) 10–6000 IU/ml, migration was measured by sequential photography. Proliferating cells were quantified after detection by immunocytochemistry (Ki 67 antibody, Dako; specific for non-G₀ cells). Wound healing occurred by movement of the whole cell sheet, migration of individual cells, and cell proliferation at the wound edge. rtPA enhanced cell migration and proliferation, by a dose dependent trend, but was less effective ($p < 0.001$) than either fetal calf serum or endothelial cell growth factor (30 µg/ml, Sigma). A combination of rtPA and fetal calf serum (supplying plasminogen) had a synergistic effect on cell migration ($p < 0.001$). We have shown that rtPA enhances coronary artery and aortic endothelial cell migration in vitro. This effect is due to the action of tPA alone as well as to migration enhancement by plasmin. Endothelin produced during hypoxia induces endothelial release of tPA. Endogenous and administered tPA bind rapidly to endothelial cells in the presence of fibrin and resultant protection from circulating tPA inhibitors.

These results suggest that the role of tPA in coronary artery disease is not only fibrinolytic, but that it may also promote endothelial repair in the coronary artery.

White cell accumulation in infarction and its inhibition by adenosine

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White cell release products may play an important part in the extension of ischaemic damage after myocardial infarction. White cell counts are known to increase in peripheral venous samples after infarction, but whether leucocytes accumulate within the infarct zone is less clear. In an open chested pig model, myocardial infarction was produced by ligation of the left anterior descending coronary artery. Areas at risk of infarction were determined by scanning of thallium-201 injected intravenously five minutes following occlusion. White cells labelled with technetium-99m were injected intravenously into 11 pigs before infarction and in a further 11 pigs at five minutes after occlusion. Pigs were killed at 30 minutes ($n = 10$), or two hours ($n = 12$) after occlusion, and the hearts extracted, opened, and imaged on a gamma camera. Paired blocks of myocardium were taken from the infarct zone and regions of normal myocardium. Mean thallium uptake within the infarct zone was 11–23% of normal. At 30 minutes after occlusion, within the infarct area, technetium-99m labelled white cell activity was seen predominantly from accumulation of labelled cells injected before infarction (120 (24)% of activity within normal myocardium) compared to those injected post occlusion (79 (39)%). By two hours, technetium-99m white cell accumulation had increased in the infarct zone, particularly from labelled cells injected before occlusion (235 (69)% *v* 178 (93)%). This accumulation of leucocytes within the infarct was inhibited by earlier infusion of either adenosine (150 $\mu\text{g/kg/min}$; $n = 5$ or an A_2 adenosine agonist, CGS 21680 (0.25 $\mu\text{g/kg/min}$; $n = 6$ (39 (21)% and 45 (15)%).

These results showed that white cell accumulation occurs with infarcted myocardium and that this may occur by a combination of trapping and migration of white cells. This may be inhibited by adenosine, a substance known to be released by the ischaemic myocardium.

Deletion within chromosome 22q11 is an important cause of isolated heart defects and the cause of over 90% of cases of DiGeorge syndrome

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We have studied 33 children with DiGeorge syndrome (DGS) (immunodeficiency, hypocalcaemia, outflow tract heart defects, dysmorphic facial appearance). The cardiac lesion was interrupted aortic arch in 16, tetralogy of Fallot or pulmonary atresia in eight, truncus arteriosus in three, pulmonary valve stenosis in two, secundum atrial septal defect in one, an aortic coarctation with atrioventricular septal defect in one, ventricular septal defect in one, and an aberrant right subclavian artery in one. An interstitial deletion of chromosome 22q11 was visible in 9/33 on high

resolution chromosome analysis. Molecular genetic analysis detected submicroscopic deletions of 22q11 in a further 22 cases. Thus we have detected 22q11 deletions in over 90% of DiGeorge syndrome cases. No other chromosomal abnormalities were found in this series. A prospective study of children referred to our regional cardiothoracic centre has identified nine cases of interrupted aortic arch over two years. Five of these developed additional features and have been included in our cytogenetic and molecular genetic study of DiGeorge syndrome. Thus half of these patients with DiGeorge syndrome had interrupted aortic arch, and more than half of a prospective series of interrupted aortic arch had DiGeorge syndrome. It is suggested that children with interrupted aortic arch should receive only irradiated blood products until T lymphocyte function has been shown to be normal in order to prevent graft versus host disease. Four families where a parent with an isolated outflow tract defect has had offspring with more severe cardiac defects, including one case of DiGeorge syndrome, have been identified. Deletions within 22q11 were identified in the affected persons in all four families.

Chromosome 22q11 deletions are an important cause of major heart defects that can recur within families.

Coarctation of the aorta: difficulties in prenatal diagnosis

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The diagnosis of coarctation of the aorta in the fetus is usually suspected when there is a disparity between the relative sizes of the left and right heart structures. These findings, however, can also be detected in some fetuses in whom there is no evidence of a coarctation postnatally, so that this diagnosis can be impossible to predict or definitively exclude in every case. Furthermore, in early pregnancy, the relative sizes of the left and right sides of the heart may appear normal despite the presence of a coarctation lesion. Over a 10 year period, the diagnosis has been correctly made in 54 fetuses, suspected but not proved in 24 and overlooked prenatally in nine. The echocardiograms of these 87 fetuses were retrospectively examined to establish diagnostic criteria for this condition in fetal life. Measurements of the ventricular widths, diameters of the great arteries, or the diameters of the atrio-ventricular valvar orifices, did not allow clear distinction between cases that definitely had a coarctation and those in whom the diagnosis was not proved. The appearance of the aortic arch, particularly in the horizontal projection, was more helpful in distinguishing cases of coarctation, although this was not foolproof. In cases where the arch was adequately imaged, a hypoplastic arch enabled correct diagnosis to be made in 80% of proved coarctations. The arch was of normal appearance in 75% of unproved cases and in 67% of cases overlooked prenatally. The most severe forms of coarctation are associated with relative hypoplasia of the left heart structures compared with the right and a correct diagnosis can be made in early pregnancy. The milder forms of coarctation are, however, consistent with a normal early fetal echocardiogram. In late pregnancy, it may be impossible to categorically exclude coarctation, as the right heart structures may appear larger than the left in the normal fetus after 28 weeks.

True incidence of cardiological abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment of 118 patients

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Noonan syndrome is one of the most common syndromes in paediatric cardiology practice, yet the incidence of cardiac abnormalities is unknown largely because of difficulties with: (a) assembling a substantial unbiased cohort, (b) phenotypic diagnosis, and (c) defining the common accompaniments—pulmonary stenosis and hypertrophy of left and right ventricles. These difficulties have been overcome by randomly selecting 145 patients from the Noonan Syndrome Society (United Kingdom), using photoanthropometric analysis by two geneticists, defining pulmonary stenosis as Doppler > 3 m/s or previous intervention, and left or right ventricle hypertrophy as end diastolic thickness > 2 standard deviations (SD) from normal controls ($n = 84$). Of these 145 there were 27 genetically atypical, thus 118, age range one month–41 years (mean 10.3 years) were studied. Pulmonary stenosis was present in 28 (24%) but Doppler was > 2 SD from normal in 42 others. Left ventricular hypertrophy was found in 29 (25%), none of whom had pulmonary stenosis, and was severe (> 1.7 cm) and diffuse in five, confined to the anterior septum in 19, and a discrete subaortic shelf in five others. Severe left ventricular outflow obstruction was uncommon, range 1.4 to 4.0 m/s (mean 2.1). Hypertrophy of the right ventricle was documented in 20: 7/20 had pulmonary stenosis and eight had left ventricular hypertrophy. Other abnormalities were atrial septal defect (9%) and mitral valve prolapse (3%).

The detailed characterisation of the cardiological problems in Noonan syndrome is an aid to both phenotypic diagnosis and genetic counselling, and is a prelude to any natural history studies or gene linkage analysis. Echocardiographic assessment of all patients with the Noonan phenotype is mandatory.

Pregnancy in cyanotic congenital heart disease: maternal complications and factors influencing successful fetal outcome

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A total of 416 patients with congenital heart disease had 822 pregnancies; 45 patients who were cyanosed (operated and unoperated) had 96 pregnancies when aged 15 to 41 (mean 24). Medical terminations were excluded. Ten patients (22%) had prenatal complications from failure (eight patients) and supraventricular arrhythmias (two patients). Perinatal complications occurred in four patients (9%); bacterial endocarditis in two, with one death after late diagnosis, pulmonary embolism in one, and cerebral embolism

in one. Of 96 pregnancies, 40 (42%) resulted in a live infant, two with congenital heart disease. Only 16 infants were full term with a mean weight of 2575 g. Fifty four (56%) miscarriages occurred at six weeks to five months. Two babies stillborn at eight months had congenital heart disease. The following factors were examined for their predictive relation with successful outcome: (a) basic anomaly in mother, divided into four groups: (A) tricuspid atresia or single ventricle, (B) pulmonary atresia or tetralogy of Fallot, (C) Ebstein's Anomaly plus atrial septal defect, (D) corrected transposition plus ventricular septal defect and pulmonary stenosis; (b) haemoglobin at beginning of pregnancy; (c) systemic arterial oxygen saturation; (d) age; (e) ability index; (f) previous surgical shunt. In a univariate analysis, age and presence of a shunt were not significantly associated with foetal outcome, whereas haemoglobin and arterial oxygen saturation were each strongly related ($p < 0.0001$). From multivariate logistic regression analysis an adjusted haemoglobin value was derived in which disease group A was equivalent to an additional 2 g/dl, and the presence of a shunt was equivalent to a reduction of 1 g/dl. The resulting score was strongly associated with the risk of miscarriage. A similar rule was derived for arterial oxygen saturation, confirming that it is the lack of oxygen rather than hyperviscosity that is the cause of foetal death.

Although there is a high complication rate in the pregnant cyanotic patient, the risks to the mother and foetus may be minimised with optimal, combined informed cardiological and obstetric care.

Coronary artery anatomy in transposition of the great arteries: is diagnosis by echocardiography accurate?

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Variations in the anatomy of the coronary arteries are well recognised in complete transposition of the great arteries. The arterial switch operation is the treatment of choice and involves relocation of the coronary arteries. We wished to establish the accuracy with which echocardiography could be used to identify coronary artery anatomy. In our series, unusual coronary artery anatomy was the cause of death in 2.9% (4/138 patients). Coronary artery anatomy was assessed prospectively by cross sectional echocardiography in 53 consecutive infants with transposition of the great arteries. A Hewlett-Packard Sonos 500 and a Ving-Med 750 with a 5 MHz short focus sector scanner were used. The images were taken in a short axis high parasternal view, augmented with use of cine loop and slow motion replay, coded and recorded. Comparison was made with the findings at operation. The mean time taken to record coronary artery anatomy was 3.8 min (maximum 13 min) although repeat imaging after balloon atrial septostomy was required in five. By the classification of Yacoub *et al*, we correctly coded 42/45 of those with type A, 1/1 type B, 0/0 type C, 1/2 type D, 2/3 type E, and 1/2 that were unclassifiable. The sensitivity for identifying abnormal coronary arteries was 63% and specificity was 93%.

Echocardiography can be used to determine coronary artery anatomy in transposition of the great arteries. This may facilitate planning of the operative procedure by the surgeon.

Congenital heart disease in adults: respective roles of magnetic resonance imaging and transoesophageal echocardiography?

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Conventional diagnostic techniques are often inadequate in defining the complex anatomy and physiology in adults with congenital heart disease. This prospective study reports the diagnostic value of magnetic resonance imaging (MRI) and transoesophageal echocardiography (TOE) in 18 patients, 14 operated and four unoperated, aged 23–57 (mean 36), with tetralogy of Fallot in six, single functional ventricle in five, pulmonary hypertension in two, transposition of the great arteries in one, corrected transposition in one, aortic coarctation in one, common arterial trunk in one, and atrio-ventricular septal defect in one. They all had unresolved diagnostic questions remaining after a routine clinical evaluation which included transthoracic echocardiography. The MRI used a 0.5 Tesla magnet to obtain multiplane spin echo images and phase shift velocity maps; TOE used a single plane 5 MHz probe. A total of 102 predefined questions were answered by MRI and TOE, of which 54% were answered by MRI alone, 46% by TOE alone, and 76% by their results combined. Also, TOE and MRI jointly produced 14 new unexpected findings. With a simple scoring system, MRI was superior to TOE in showing pulmonary artery anatomy, extracardiac shunts and conduits, and the ventriculoarterial connexion. Velocity maps were important in quantifying stenoses of extracardiac conduits; MRI was technically inadequate in patients with atrial fibrillation and gave false positive findings of intravascular clot (one patient), and large atrial septal defect (two patients); TOE was good at showing the atrial situs and septum, the atrio-ventricular valves and coronary artery anatomy, but poor at showing the right ventricular outflow tract. Both TOE and MRI in combination were most valuable in patients with more complex anatomy, and least helpful in those with less complex anatomy (for example Fallot), when the main unanswered questions were the pulmonary artery pressure or the presence of coronary atherosclerosis.

In complex cases of congenital heart disease in adults, MRI and TOE combined are prerequisites for definitive anatomical and physiological diagnosis as they provide important and complementary information.

Permanent pacing in cardioinhibitory malignant vasovagal syndrome—the Westminster experience

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Thirty seven patients (mean age at implant 62.3 (SD 14.5); 21 men with cardioinhibitory malignant vasovagal syndrome have been managed with permanent pacemakers at the Westminster Hospital. They presented with syncope (mean (SD) 14.4 (29), frequency 3.4 (5.3)/year) and after conventional investigation they remained undiagnosed and without a generally accepted indication for pacemaker implantation. All developed vasovagal syncope with

cardioinhibition (heart rate at syncope < 60 beats per min) during tilt testing performed according to the Westminster protocol (head up tilt at 60° on a footplate support for 45 minutes or until syncope intervenes). Dual chamber pacemakers were implanted in 37 (95%) and VVI pacemakers in the remaining two (5%). Follow up since implantation is complete for all patients (39 (19.9) months). Symptomatic improvement has been achieved in 84%, syncope abolished in 62%, and complete resolution of all symptoms is reported by 36%. The collective syncopal burden of these 37 patients has been reduced from 125.8 episodes each year to 12.6 episodes each year. One patient died from a myocardial infarction. The patients who have remained free of syncope since implant were younger (57.7 v 69.9 years, $p < 0.02$) and had lower supine systolic blood pressure measurements at rest (135 v 162.7 mm Hg $p < 0.001$) compared with those who have continued to experience syncope. Otherwise no demographic, clinical, investigative, or pacing variables suggested a more favourable outcome after pacing.

Our experience suggests that permanent pacing for cardioinhibitory vasovagal syncope is a reasonable therapeutic strategy. Over the mean follow up of 39 months, however, 38% of patients have experienced further syncope, and retrospective analysis failed to identify any preimplant variable which individually discriminates these patients from those who have remained free from syncope.

Sounds in the superior vena cava caused by presystolic flow reversal: a sign of right ventricular disease

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The classical S_4 is due to atrial flow into a diseased ventricle, but for some presystolic sounds, venous origin has been postulated. We therefore recorded phonocardiograms over the precordium, upper right sternal edge, and jugular veins with simultaneous electrocardiograms, Doppler flow in the superior vena cava, and atrioventricular valve flow in all patients referred for echocardiography over a nine month period. In 27 patients (10 with pulmonary hypertension, five dilated cardiomyopathy, three pericardial constriction, three cardiac amyloid, two hypertrophic cardiomyopathy, one aortic stenosis, one subaortic stenosis, one pericardial effusion with tamponade, and one after Mustard operation) presystolic sounds were recorded from a localised area (only over the superior vena cava or jugular veins). Each was associated with a rapid blood flow reversal in the superior vena cava, evident on Doppler. Presystolic sounds occurred at a point of change in acceleration (mean change = $17.1 (6.9) \text{ m/s}^2 = 1.7 \text{ g}$). The onset of the sound coincided with peak retrograde velocity in 18 cases, peak forward velocity in six, and with the onset of retrograde flow in three. In 19 cases no atrial flow across either atrioventricular valve could be detected, excluding a classical S_4 . In eight cases with atrial tricuspid flow, the sounds could only be recorded over the jugular veins.

Presystolic sounds may be recorded over the superior vena cava and jugular veins from patients with pulmonary hypertension and ventricular disease. They appear to originate from a rapid blood flow reversal in the superior vena cava rather than atrioventricular flow, and are thus quite different from the classical S_4 .

Familial aggregation of idiopathic dilated cardiomyopathy: Variable clinical phenotypes and autosomal dominant pattern of inheritance in 14 families

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To establish a pattern of inheritance in familial dilated cardiomyopathy we assessed 117 apparently healthy relatives of 14 patients (probands) with dilated cardiomyopathy. Criteria for selection of pedigrees was based upon the presence of documented disease (World Health Organisation definition) in at least one other member of the proband's family. Twenty two family members were affected; 18 experienced disease related death (median age 47) with the clinical diagnosis confirmed at necropsy in 13. All 117 apparently healthy relatives were screened with a standard 12 lead electrocardiogram and cross sectional echocardiogram and were classified either as unequivocally normal or as carriers. The latter had either an abnormal electrocardiogram or at least one echocardiographic measurement of left ventricular cavity dimension, or % fractional shortening outside 2 SD of normal (measurements corrected for body surface area). Fourteen of the 117 relatives (12%) had systemic hypertension and were excluded from the study. Thirty two of the remaining 103 relatives (31%) were classified as carriers and underwent 24 hour Holter monitoring and maximal treadmill exercise (Naughton protocol). Of these 32 relatives, four (aged 45 (21) had only abnormal electrocardiograms; 18 (aged 24 (13) had normal electrocardiogram and abnormal cross sectional echocardiogram with 10 (5)% left ventricular enlargement, but % fractional shortening within the normal range; 10 (aged 41 (13)) had abnormal electrocardiogram and cross sectional echocardiogram with 16 (21)% left ventricular enlargement from normal and 26 (9)% fractional shortening. Three of these 10 relatives also had ventricular arrhythmia (Lown class III or IV).

Thus non-invasive techniques identified asymptomatic cases of familial dilated cardiomyopathy among apparently healthy relatives of patients with the disease. Pedigree analysis was most consistent with an autosomal dominant pattern of inheritance with a high degree of penetrance.

Value of time and frequency domain and spectral temporal mapping analysis of the signal-averaged electrocardiogram in identification of patients with hypertrophic cardiomyopathy at increased risk of sudden death

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Late potentials detected by the signal-averaged electrocardiogram (SAECG) identify postinfarction patients at risk from sustained ventricular tachycardia and sudden death. Hypertrophic cardiomyopathy is also associated with increased risk of sudden death. In adults, episodes of non-sustained ventricular tachycardia on ambulatory electrocardiographic monitoring are a marker of high risk patients. In children and adolescents, however, no reliable

electrocardiographic marker exists and clinical features have low predictive accuracy. The prognostic value of the SAECG in hypertrophic cardiomyopathy has not been systematically evaluated. In this study, we examined the relation of detailed time domain, frequency domain, and spectral temporal mapping analysis of the SAECG and clinical and echocardiographic features, and the results of 48 hour ambulatory electrocardiographic monitoring in 121 consecutive patients with hypertrophic cardiomyopathy but no cardioactive medication. Non-sustained ventricular tachycardia on Holter monitoring was recorded in 27 (23%) patients. Late potentials were detected on the time domain SAECG in three (11%) patients with ventricular tachycardia *v* three (3%) without (NS). Of the SAECG variables, reduced ($< 150 \mu V$) voltage of the initial 40 ms of the signal averaged QRS complex was the best predictor for non-sustained ventricular tachycardia (sensitivity, 95%; specificity, 74%; positive predictive value, 64%; negative predictive value, 97%). The frequency domain analysis and spectral temporal mapping of the SAECG did not improve the identification of patients with ventricular tachycardia. Eight patients (of whom seven were ≤ 30 years of age) experienced catastrophic events: three died suddenly and five were resuscitated from out of hospital ventricular fibrillation. None of them had an abnormal SAECG.

Alterations of the initial portion of the signal-averaged QRS complex identified adults with hypertrophic cardiomyopathy and non-sustained ventricular tachycardia on ambulatory monitoring, but the SAECG was not useful in identifying those young patients who suffered cardiac arrest.

Enteroviral serology in idiopathic dilated cardiomyopathy

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Serological studies provide the principal supporting evidence for a pathogenic role of enteroviral infection in human idiopathic dilated cardiomyopathy (DCM). These studies, however, have failed to study matched controls taken at the same time and from the patients' environment and to distinguish between active and previous viral infection. In this study we applied a reverse radioimmunoassay technique for the detection of coxsackie B virus specific-immunoglobulin M (CBV IgM) (B1-5) to sera taken from patients with DCM at the time of diagnosis ($n = 83$), matched controls ($n = 17$), and unmatched family members ($n = 94$). Sera from 32 patients with DCM and 11 matched controls was also assessed for the presence of a common enteroviral antigen (VP1) believed only to be present during persistent active viral infection. Patients with DCM (mean age 44.2, range 17 to 74) had been symptomatic for 38.6 (49) months, 18 (22%) gave a history of a preceding acute viral illness and three had features of myocarditis on endomyocardial histology. Positive CBV IgM serology was seen in 24 (29%) patients with DCM, three (18%) matched controls ($p = 0.17$), and 16 (17%) unmatched controls ($p = 0.03$). No association was found in patients with DCM between the presence of positive CBV IgM serology and clinical or histological features. Serological responses were most commonly against serotypes B2 and B5; however multitypic responses to a num-

ber of different viral serotypes were common (14/48, 29%). These responses were similar in patients with DCM and control groups. High concentrations of VP1 were detected in 7/32 (22%) patients with DCM compared with 0/11 matched controls ($p = 0.1$). There was no association between the presence of high concentrations of VP1, clinical and histological features, or positive CBV IgM ($R = 0.1$, $p = 0.8$).

This study shows that (a) CBV IgM is common within the general population, (b) a higher prevalence of CBV IgM in patients with DCM compared with unmatched controls, (c) a non-significant trend towards a higher prevalence of CBV IgM and VP1 in patients with DCM compared with matched controls, and (d) no association in DCM between positive enteroviral serology and clinical or histological features.

Mechanisms of intracellular pH recovery in perfused heart

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The sodium-hydrogen (Na^+/H^+) antiport has been suggested as the predominant, or only mechanism facilitating recovery from an intracellular acidosis in cardiac muscle. In other mammalian cells external bicarbonate (HCO_3^-) dependent acid equivalent extrusion and proton (H^+) coupled lactate efflux can also participate. We have examined the contributions of these three mechanisms to the recovery of pH_i and contraction after an acid load induced at normal extracellular pH with either an ammonium chloride (NH_4Cl) prepulse or 1-lactate, in the Langendorff-perfused ferret heart. Hearts were perfused with either HCO_3^- or nominally HCO_3^- free (HEPES) buffer. The Na^+/H^+ antiport was blocked by the specific inhibitor ethylisopropylamiloride. pH_i was estimated using ^{31}P nuclear magnetic resonance spectroscopy with isovolumic left ventricular developed pressure being recorded throughout. Hearts were exposed to either NH_4Cl (10 mM) or 1-lactate (10 mM) for 10 min and rates of recovery of pH_i from 6.90 after withdrawal of NH_4Cl or 1-lactate calculated. Results are expressed as mean (SE). After an intracellular acidosis induced by an NH_4Cl prepulse the initial rate of recovery of pH_i in Hepes solution was slower (0.013 (0.005); $n = 14$) than in HCO_3^- solution (0.024 (0.006); $n = 13$). Na^+/H^+ antiport inhibition delayed pH_i recovery in HCO_3^- solution (0.012 (0.003); $n = 9$) and blocked pH_i recovery in Hepes solution (< 0.001 ; $n = 10$). Recovery of left ventricular developed pressure was similar to that of pH_i with Na^+/H^+ antiport inhibition causing slowing of recovery in HCO_3^- solution and blocking recovery in Hepes solution. After 1-lactate withdrawal pH_i recovered more rapidly (0.047 (0.005); 13) as did left ventricular developed pressure than after an NH_4Cl prepulse and both recovered fully in the absence of external HCO_3^- during Na^+/H^+ antiport inhibition. H^+ -coupled lactate efflux can account for the differences in recovery after 1-lactate when compared with recovery after NH_4Cl prepulse.

The Na^+/H^+ antiport and an external HCO_3^- dependent mechanism are therefore both important in the recovery from intracellular acidosis in the intact perfused ferret heart. When intracellular lactate is high, for example, after ischaemia, H^+ -coupled lactate efflux could also contribute to this recovery.

Characterisation of the angiotensin receptor expressed by cells transfected with a plasmid containing the AT_1 cDNA

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Angiotensin II (AII) is an important peptide in cardiovascular disease, yet little is known about regulation of its receptor at the molecular level. Two AII receptor subtypes, AT_1 and AT_2 , have been identified using non-peptide antagonists and the complementary DNA (cDNA) encoding the AT_1 receptor has been isolated. We have examined the pharmacological profile and signal transduction pathways of this cloned receptor transiently expressed in COS-M6 cells. Transfected COS-M6 cells expressed high specific (^3H)-AII binding (K_d of 7.1 (0.5) nM and B_{max} of 1.9 (0.5) pmol/mg protein, $n = 5$). Competition binding assays showed that the receptor displayed high affinity for AII, AIII, and the AT_1 selective antagonist DuP753 (K_i values of 2.4, 13.6, 12.1 nM, respectively), but low affinity for the AT_2 selective drugs CGP42112A and PD123177 (K_i values > 1000 and > 10000 nM respectively). The AT_1 receptor has been reported to couple to two signal transduction pathways, the mobilisation of intracellular calcium (Ca^{2+}_i) and inhibition of adenylate cyclase. Addition of AII (0.1 μM) to transfected cells resulted in a transient increase in (Ca^{2+}_i) (from 57 (8) to 303 (26) nM, $n = 20$). By contrast, AII (0.1 μM) failed to attenuate forskolin (1 μM) induced increases in intracellular cyclic AMP, suggesting that the cDNA encodes an AT_1 receptor coupled to the mobilisation of (Ca^{2+}_i), but not coupled to inhibition of adenylate cyclase. Cells not transfected did not express AII receptors, nor a calcium response to AII.

We have transiently expressed the angiotensin AT_1 receptor and defined its pharmacology and coupling to mobilisation of (Ca^{2+}_i), and can now therefore study its structure and regulation using site directed mutagenesis.

Programmed cell death is a mechanism of senescence of human endothelial cells in culture

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Programmed cell death (apoptosis) has been shown to be an important mechanism of physiological senescence in a number of cell types including neutrophils, lymphocytes and most epithelial cell types. The exact cellular mechanisms of apoptosis remain unclear, but a final common event is activation of an endogenous endonuclease, causing highly organised digestion of double stranded DNA at internucleosomal sites, which produces a characteristic "ladder pattern" on DNA electrophoresis. This pattern is thought to be specific to cells dying by apoptosis rather than by necrosis. Endothelium grown from a number of sources appears to have a finite life, limited to a specific number of population doublings in culture. It was investigated whether apoptosis is the mechanism of death in human umbilical vein endothelial cells (HUVEC) grown to end of life in culture; HUVEC were grown in culture with medium 199 supplemented with heparin and endo-

thelial cell growth supplement. Growth appeared to cease after the third passage of the cells in culture. The cells were rounding up and some had floated off into the supernatant medium. Cells were harvested both from the medium and separately from the floor of the culture flasks; DNA was extracted using a phenol/chloroform technique with proteinase K digestion; and RNA was removed using an RNase A digestion. One per cent agarose gel electrophoresis showed no evidence of DNA cleavage in the cells that remained adherent but a characteristic DNA ladder was seen from the cells in the supernatant. A spontaneously immortalised HUVEC line (ECV 304) was also studied. These cells, which retain phenotypic characteristics of endothelium, have been grown in culture for over a hundred passages. Exposure to tumour necrosis factor (200 ng/ml) was without morphological effect and no DNA fragmentation could be found. Calcium ionophore (A23187) (10 μ M) as well as the protein kinase C antagonist H-7 (50–200 μ M) caused rounding up of these cells and detachment from the culture plate but no DNA fragmentation.

These results suggest that apoptosis may be an important mechanism limiting the absolute life span of endothelial cells.

Flow cytometry of whole blood: a method for analysing platelet activation in cardiovascular disease

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Platelets are important in the pathogenesis of cardiovascular disease. Activation of platelets results in thrombus formation and the release of platelet derived growth factors, vasoactive and pro-coagulant molecules. Assessment of platelet activation by aggregometry is insensitive, whereas detection of released β thromboglobulin or platelet factor 4 is subject to technical error and only measures platelet degranulation. Platelets are activated by a number of physiological agonists. Weak agonists such as adrenaline or ADP cause a conformational change in the glycoprotein (GP) IIb–IIIa complex, exposing a binding site for fibrinogen. Strong agonists such as thrombin or vessel wall collagen cause degranulation that results in the translocation of granule membrane to the platelet surface, bringing with them specific membrane proteins which appear as neo-antigens, and can be detected with monoclonal antibodies (MAbs). Two such MAbs are described, RFAC4 recognises the GP53 antigen on lysosomal membranes and RFAC2 recognises the GMP140 antigen of the α granule. These MAbs were labelled with fluorochrome and used in a whole blood flow cytometric assay to detect activated platelets minimising the artefactual activation in vitro. Fibrinogen bound to activated GPIIb–IIIa was detected using an anti-fibrinogen antibody. None of the activation markers was expressed on resting platelets from normal subjects ($n = 15$). After stimulation with ADP >80% of normal platelets bound fibrinogen, 10% bound RFAC4, and <2% bound RFAC2. When stimulated with throm-

bin >90% of normal platelets expressed all three markers. Platelets from patients with different thrombotic disease states showed different patterns of expression of the three activation markers. Blood from patients with peripheral vascular disease ($n = 13$) contained platelets with raised GP53 expression. This increased expression was enhanced when ADP was added to the blood ex vivo. By contrast, patients with unstable angina ($n = 6$) showed more activation, with raised expression of all three markers.

The differential expression of the various activation markers can be used to assess the extent of platelet involvement in various thrombotic states and to gain information as to the likely cause of activation in vivo. This information will lead to a more rational approach to anti-platelet therapy.

Electrocardiographic waves following the T wave in patients with idiopathic ventricular tachycardia: a surface manifestation of afterdepolarisations?

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The mechanisms of arrhythmia in patients with idiopathic ventricular tachycardia remain unclear, though there are suggestions that the mechanism may be triggered by activity in patients with exercise induced ventricular tachycardia. We have examined the electrocardiogram during exercise tests in 20 patients with idiopathic ventricular tachycardia for evidence of a triggered activity mechanism. Eight patients (six with exercise induced ventricular tachycardia) showed prominent deflections either in the tail portion of the T wave, or after the T wave in the position of the classical U wave. Visualisation of these deflections was easier using high gain (20 mm/mV) and the filtered average complex, available on the Marquette treadmill exercise test machine. These deflections were most clearly seen in chest leads V2 to V4 in all patients and although clearly visible at rest, became larger in the recovery period after exercise. During the exercise test, the deflections became difficult to identify because of the presence of the next P wave in the tail of the T wave. The mean amplitude of the deflections was 2.4 (0.8) (SD) mV, and the amplitude of the associated T wave was 3.9 (2.5) mV. The time from the Q wave to the peak to the T wave was 287.5 (68.4) ms and from the Q to the peak of these deflections was 447.5 (72.7) ms. The time from the Q to the next P wave was greater than 600 ms in all cases where the measurements were performed. In six patients, ventricular extrasystoles were identified in association with the deflections; the Q to extrasystole coupling interval was never more than 40 ms different from that of the Q to peak of the deflection. The deflections were not completely abolished by calcium antagonists or β blockers. We propose that these deflections may represent a surface manifestation of membrane potential oscillations after the action potential, i.e. afterdepolarisations, which are identifiable by use of the averaged, filtered, high gain electrocardiogram.

The close relation in timing to ventricular extrasystoles suggests that these may play a part in triggered ventricular extrasystole activity.

Relation of ventricular ectopic activity to spectral measures of heart rate variability in patients with idiopathic ventricular tachycardia

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The autonomic nervous system appears to have an important role in the genesis of ventricular arrhythmias in patients after myocardial infarction and in idiopathic ventricular tachycardia. Roughly 40% of patients with idiopathic ventricular tachycardia have the arrhythmia induced at exercise. Spectral measures of heart period variability allow a non-invasive estimate of the activity of sympathetic and parasympathetic efferents to the heart. We have studied the relation of hourly spectral measures of heart period variability to the occurrence of ventricular extrasystole in 20 patients with idiopathic ventricular tachycardia (age range 17 to 60). Twenty four hour Holter tapes were obtained from patients in a drug free state and analysed on the Marquette 8500 laser Holter system. Spectral measures obtained from the heart period variability program were the low frequency components (L) (0.04–0.15 Hz) representing predominantly sympathetic tone (S) with some contribution from the parasympathetic and high frequency components (H) (0.15–0.4 Hz) representing mainly parasympathetic tone (P). High sympathetic tone was defined as $H > 12$ and high parasympathetic tone as $L > 30$. The occurrence of single ventricular extrasystoles was ignored by the program with interpolation of the RR intervals, whereas longer episodes of extrasystole are excluded. On an hourly analysis of spectral components in relation to ventricular extrasystole, extrasystoles occurred significantly more often during periods of low S and low P tone ($F = 20.5$, $p < 0.0001$). The number of extrasystoles did not differ statistically in the other combinations of S and P tone (Mean extrasystole/hour (SEM) high S and high P, 204.9 (17.7); low S and high P, 338.4 (58.9), high S and low P, 180.1 (36.8); low S and low P 612.8 (50.1). The ventricular extrasystoles were not escape beats as the coupling interval of the extrasystole to the previous normal beat was less than the previous normal to normal interval.

Ventricular extrasystoles are more frequent during periods of low sympathetic and low parasympathetic tone and are decreased in number when either sympathetic or parasympathetic activity is increased in patients with idiopathic ventricular tachycardia.

Development of late potentials after myocardial infarction is related to infarct size

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Recent studies have shown a reduction in the incidence of late potentials after thrombolysis, but the mechanism for this remains unclear. One possible explanation is that late potential development is related to infarct size, but previous studies attempting to relate late potentials to infarct size using peak creatinine kinase or its MB isoenzyme have produced conflicting evidence. A prospective study was therefore undertaken to relate late potentials measured from the signal-averaged electrocardiogram to infarct size measured by the cumulative release of α -hydroxybutyrate dehydrogenase (α -HBDH). Sixty six patients admitted with a first myocardial infarction were studied. Blood sam-

ples were taken on admission, every 12 hours for the first two days and daily for the next three days. The samples were analysed for α -HBDH activity and the area under the time activity curve up to 72 hours was calculated as an index of infarct size. Signal averaged electrocardiograms were performed on day 1, day 3, day 7, and at six weeks after admission. The presence of late potentials was assessed according to conventional time domain analysis criteria. The incidence of late potentials overall was 18.6% on day 1, 22.7% on day 3, 36.5% on day 7, and 21.7% on day 42. The mean area under the curve of the patients' late potential positive and late potential negative on each of these days was 30 443 v 18 254 on day 1 ($p < 0.05$ by t test), 31 689 v 17 077 on day 3 ($p < 0.05$), 27 148 v 18 970 on day 7 (non-significant), and 36 680 v 17 613 on day 42 ($p < 0.01$).

Late potentials are related to infarct size. By inference reduction of infarct size by reperfusion may be the mechanism by which thrombolysis reduces the incidence of late potentials.

Magnesium prolongs ventricular action potential duration in the denervated heart

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The empirical use of magnesium (Mg) as an anti-arrhythmic agent has been reported for over 50 years, but the mechanism of such beneficial effect remains obscure. We postulated that subtle changes in ventricular electrophysiology would be more apparent in the denervated heart, known to be supersensitive to catecholamines and adenosine. Ventricular monophasic action potentials were recorded from the right ventricular pacing in 10 of 12 unselected cardiac transplant recipients (age 37 to 61 y). Median time from transplantation was 15 weeks (range 1 to 35). All patients were receiving standard immunosuppressive treatment and none was treated with anti-arrhythmic drugs. Serum potassium and calcium concentrations were within normal limits. Ventricular action potential duration was recorded and the ventricular effective refractory period established at two paced rates, before and after intravenous administration of 8 mmol magnesium sulphate. A 12 lead electrocardiogram was recorded before and after each procedure. Mean (SD) serum magnesium concentration rose twofold; 0.69 (0.08) v 1.31 (0.23) mmol/l ($p < 0.001$). There was a strong trend towards prolongation of the ventricular action potential duration in response to Mg (95% CI, 1.3 to 12.0 ms; $p = 0.11$). No consistent effect on ventricular effective refractory period was noted. Duration of QRS interval was prolonged in eight out of 11 patients ($p < 0.07$; paired t test; 90% CI, 0.8 to 13.6 ms), showing, or exacerbating a right bundle branch block pattern. There was no significant difference in the QTc interval. Baseline hypomagnesaemia (serum Mg < 0.70 mmol/l) was concurrent in five subjects; there was no difference in ventricular action potential at baseline pacing between hypo- and normo-magnesaemic recipients. Mean ventricular effective refractory period, however, during both pacing protocols was significantly shorter both before and after Mg in the hypomagnesaemic group ($p < 0.05$; ANOVA).

Intravenous magnesium measurably prolongs ventricular action potential in the denervated human heart and this effect is independent of baseline magnesium. Such effects are predicted from single cell studies, but have not been previously shown in man.

A 10 year review of the management of false aneurysms after transfemoral arterial catheterisation

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False aneurysms of the femoral artery are an infrequent complication of transfemoral arterial catheterisation. They may be the cause of significant morbidity but little is documented about their clinical course and the results of surgical repair. The management by one vascular surgery unit of these false aneurysms over the decade commencing 1 January 1980 was reviewed. Fifty five false aneurysms were identified; three after 3396 radiological procedures (0.09%) and 52 after 11 255 cardiac procedures (0.46%). Three false aneurysms did not require surgical repair and one patient died before treatment. Twenty false aneurysms remained stable, 18 continued enlarging, and 13 had ruptured at the time of operation. Aetiological factors and postoperative complications of the different groups were analysed using the χ^2 test. The mean time to presentation for stable false aneurysms was 4.05 days (SD 5.46), for enlarging false aneurysms 27 days (66), and for ruptured false aneurysms 2.75 days (1.65). Postoperative complications developed in four (20%) stable, four (22%) enlarging and seven (58%) ruptured ($p < 0.05$). There was one postoperative mortality but this resulted from the complications of subsequent cardiac surgery. Rupture of false aneurysms was associated with raised liver function tests (LFTs) on admission ($p < 0.01$), pre-catheterisation warfarin therapy ($p < 0.05$) and peripheral vascular disease ($p < 0.05$).

False aneurysms often present late after transfemoral arterial catheterisation. Ruptured false aneurysms are seen earlier than non-ruptured false aneurysms and are associated with significantly greater morbidity. Patients with false aneurysms who have elevated LFTs, peripheral vascular disease, or were taking warfarin are at an increased risk and merit closer observation and perhaps earlier intervention.

Clinical features and treatment of patients with paroxysmal atrial fibrillation: the CRAFT multicentre registry

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Epidemiologic data of clinical features, and survey of the use of antiarrhythmic drug therapy in patients with symptomatic paroxysmal atrial fibrillation were obtained. Clinical and echocardiographic data on all eligible outpatients seen by cardiologists at the 10 centres participating in the CRAFT (Controlled Randomised Atrial Fibrillation Trials) studies were registered. All 113 patients had had at least one episode of atrial fibrillation in the previous six months. Sixty two (55%) were men, mean age 56.0 (SD 13.9) and 51 were women, mean age 63.8 (SD 11.9). Symptom frequency with no antiarrhythmic treatment was similar between the sexes: 15 (13%) had no episodes, 36 (32%) had 1 to 2 episodes, and 61 (54%) had more than two episodes in two months. Clinical findings (cardiovascular history, physical examination) were normal in more men than women: 37 (60%) *v* 20 (39%) had no abnormality ($p < 0.05$), 13 (21%) *v* 16 (31%) had minor

abnormalities such as untreated hypertension or "benign" murmurs, and 12 (19%) *v* 15 (29%) had significant abnormalities. Detailed echocardiographic findings were available for 45 men and 32 women: again, these were entirely normal in a greater proportion of men than women (26 (59%) *v* 13 (40%), $p < 0.05$). The difference was entirely accounted for by a greater incidence of mitral valve prolapse among the women (six (19%), *v* one (2%)): the incidence of other minor valve abnormalities (16%), significant valvular disease (16%), and myocardial disease (9%) was identical between the sexes. Left atrial diameter was increased (4.0 cm or greater) in eight women (25%) and three men (7%). Sixty seven patients (59%) were taking prophylactic antiarrhythmic drugs. Of these, 30% were taking digoxin, 7% class 1a drugs, 12% class 1c drugs, 15% β blockers, 12% sotalol, 7% amiodarone and 9% combinations. The class of symptom frequency was improved by treatment in 25 (37%), unchanged in 35 (52%), and worsened in 7 (10%).

Paroxysmal atrial fibrillation occurs at a lower age and more often as an isolated finding in men compared with women. Most treatment is with drugs that have not been formally evaluated for this condition, and controlled trials of these agents are needed.

Coronary artery bypass grafting; identification of "fast track" patients

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Availability of intensive therapy beds often determines the throughput of cardiac surgery. The prospective identification of patients who spend less than 24 hours in intensive therapy, "fast track" patients, would allow optimal bed usage and efficient planning of operating lists. Potential fast track patients were identified from 421 patients (16% women, mean age 57 (8) years), admitted to intensive therapy after coronary surgery over a nine month period, according to prospectively defined criteria: good left ventricular function (ejection fraction $> 50\%$), stable angina, age < 60 , and absence of obesity (body mass index < 30), diabetes, or other serious pathology. Eighty seven (21%) patients were predicted as fast track; 79 (91%) spent less than 24 hours in intensive therapy, but four spent > 72 hours in intensive therapy. The positive predictive accuracy of these criteria for the identification of fast track patients was 91% but the sensitivity was low at 23%. Of the remaining 334 patients, 261 (78%) spent less than 24 hours in intensive therapy, 121 (36%) had unstable angina, and 87 (26%) had left main stem stenosis. The positive predictive accuracy of good ventricular function alone was 85% (75% sensitivity), one or two vessel disease was 91% (35% sensitivity), and left ventricular end diastolic pressure < 13 mm Hg was 91% (59% sensitivity). These associations were all significant ($p < 0.05$). Age, sex, left main stem stenosis, unstable angina, body mass index, diabetes, and treadmill exercise tolerance were not significantly associated with time spent in intensive therapy.

Fast track patients can be identified prospectively with high predictive accuracy from clinical criteria. The relative insensitivity of these criteria is unimportant when planning operating lists because only a subset of intensive therapy beds need to be designated as fast track. Left ventricular function, especially as measured by left ventricular end diastolic pressure, and number of coronaries diseased were the best individual predictors of fast track patients.

Angiographic and pathological features of coronary occlusive disease in cardiac transplant patients

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Coronary occlusive disease is the commonest late complication after cardiac transplantation. It has both similarities and differences compared with conventional atherosclerotic coronary disease. The pathophysiology and risk factors associated with disease development are not completely clear at present. Angiographic and pathological data for coronary occlusive disease in our cardiac transplant programme were reviewed. Of a population of 383 patients whose transplant was performed between January 1979 and June 1990, 447 coronary angiograms were available for review in 193 cardiac transplant patients. Coronary occlusive disease was defined as any evidence of disease in a primary or secondary coronary artery. The angiographic prevalence of coronary occlusive disease was 3% and 40% at one and five years respectively. Twenty six grafts failed due to coronary occlusive disease compared with 132 graft failures from all causes during this period. Thirteen of a possible 18 post mortems from patients dying from coronary occlusive disease were available. The remaining seven patients underwent cardiac retransplantation with one patient undergoing a further cardiac retransplant. Acute thrombosis was present in a large vessel in seven of 13 fatal cases undergoing necropsy (54%). Significant large vessel involvement with disease in smaller distal vessels on histological examination was present in four patients (31%). The remaining two patients (15%) had small vessel disease alone. Twelve of the 13 patients had significant cardiomegaly (cardiac weight ≥ 400 g) with a mean weight of 510 g (range 370–740 g). Risk factors associated with disease development in multivariate analysis included donor age > 40 (RR 3.22, CI 0.94–10.98, $p < 0.1$), recipient age > 50 (RR 1.74, CI 0.77–3.91, $p < 0.1$), and a previous history of ischaemic heart disease (RR 2.71, CI 1.4–5.22, $p < 0.05$).

Coronary occlusive disease is the main late complication after cardiac transplantation. Coronary thrombosis, ischaemia from large and small vessel coronary stenoses plus cardiomegaly cause graft failure in these patients.

High levels of antistreptokinase antibody and neutralisation titres from three days to three years after a previous dose of streptokinase

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Streptokinase (SK) reduces mortality in acute myocardial infarction. Its antigenicity can cause allergic reactions, or SK neutralisation, or both resulting in suboptimal or ineffective treatment. Currently, readministration of SK is not advised from five days to one year after a previous dose. We have conducted a study to determine when SK can be readministered for reinfarction by measuring both anti-

streptokinase antibody (AB) and neutralisation titres (NT) in two groups of patients: (a) early—36 patients (18 received hydrocortisone, HCO group, before thrombolysis and 18 did not, non-HCO group) whose titres were measured before and daily for at least five days after thrombolysis. (b) late—32 patients who received thrombolysis 12 to 38 months previously. Results are mean (SEM): (a) early—in 33% of non-HCO and 5.6% of HCO patients, the AB, or NT, or both were raised by day 4. One patient could neutralise 1.97 MU of SK at day 4 and 15.75 MU by day 5. Non-HCO group: day 4, AB 57 (19), NT 0.24 (0.10) MU; day 5, AB 226 (76), NT 1.33 (0.85) MU; HCO group: day 4, AB 21 (8), NT 0.13 (0.01) MU; day 5, AB 47.8 (17), NT 0.16 (0.03) MU. (b) late—16 patients (50%) had either AB ≥ 160 , or NT > 1.5 MU, or both; 12 to 17 months: AB 230 (51), NT 0.84 (0.25) MU; 18 to 29 months: AB 193 (55), NT 0.50 (0.16) MU; 30 to 38 months: AB 56 (26), NT 0.16 (0.03). Anti-SK AB and NT were correlated ($n = 255$, $r = 0.91$, $p < 0.001$).

It would be prudent to avoid the readministration of streptokinase or anistreplase between three days and at least three years two months after a previous dose.

Heart rate recovery after exercise: a new index of autonomic balance in post-infarction patients?

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Depressed baroreceptor sensitivity (BRS) is associated with an increased risk of spontaneous and inducible life threatening arrhythmias after myocardial infarction. Its assessment, however, is time consuming. As the rate of decline in heart rate after exercise is influenced by parasympathetic function, we examined whether baroreceptor sensitivity in post-infarction patients could be estimated from a record of the heart rate during the recovery period after predischARGE treadmill exercise tests. In a prospective study, 56 patients aged between 30 and 70 underwent baroreceptor sensitivity testing immediately before a maximal treadmill exercise test. Investigations were conducted between six and 11 days after infarction. Resting systolic blood pressure, peak systolic blood pressure, resting heart rate, peak heart rate, and exercise duration were recorded. A continuous plot of instantaneous heart rate against time was made throughout exercise. The rate of decline in heart rate was defined as the slope of the rapid, linear, early recovery phase and expressed in beats/min/s. Duration of exercise ranged from 90 to 623 s; depressed baroreceptor sensitivity from 1.4 to 35 ms/mm Hg (mean 9), peak heart rate from 81 to 172 beats/min, and rate of decline of heart rate from 0.05 to 1.1 beats/min/s. Depressed baroreceptor sensitivity correlated with rate of decline of heart rate ($r = 0.45$, $p < 0.01$), and with resting heart rate ($r = 0.37$, $p < 0.01$), and this regression equation was found: depressed baroreceptor sensitivity = $((10.8 \times \text{rate of decline of heart rate}) - (0.2 \times \text{resting heart rate}) + 20)$. Depressed baroreceptor sensitivity did not correlate with diastolic blood pressure, peak heart rate, or resting systolic blood pressure.

The rate of decline in heart rate after exercise may be used to assess vagal reserve. Its value in predicting sudden death needs further study.

Evidence for free radical generation (oxidative stress) in unstable angina

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The pathophysiology of unstable angina seems to involve the formation of, and then spontaneous lysis of, coronary artery thrombosis. Consequently, recurrent myocardial ischaemia reperfusion cycles may occur with the potential for free radical generation. We have, therefore, sought evidence of oxidative damage to proteins by measuring plasma reduced thiol, and lipids by measuring plasma thiobarbituric acid reactive substances, in patients with unstable angina. Unstable angina was defined as crescendo or rest ischaemic cardiac pain associated with electrocardiographic change but no rise in cardiac enzymes. Patients with chronic stable angina admitted for elective cardiac catheterisation were used as controls (for medication, smoking history, etc); a normal population was also studied. Forearm venous blood was collected at 0830 hours after an overnight fast. In unstable angina ($n = 25$; age 57 (2); nine women) mean plasma reduced thiol concentration was reduced to 419 (9) (SEM) compared with 485 (4.9) $\mu\text{mol/l}$ in patients with stable angina ($n = 24$; age 58 (2); three women) ($p < 0.01$). Plasma reduced thiol concentration in normal people was 564 (8) $\mu\text{mol/l}$ ($p < 0.01$ v both angina groups). Thiobarbituric acid reactive substances were similar in each angina group (unstable angina 10.00 (0.37) v stable angina 9.6 (0.21) nmol/l (NS)). The mean concentration of thiobarbituric acid reactive substances in normal people was 8.1 (0.21) nmol/l ($p < 0.01$ v both angina groups). The extent of coronary artery disease was not different in the two patient groups.

These data show that unstable angina is associated with oxidative damage to plasma proteins, possibly due to free radical production. Free radical activity could have detrimental effects in unstable angina by damaging endothelium and promoting thrombosis.

Significance of reciprocal ST depression on the resting and exercise electrocardiogram in patients with acute infarction treated by thrombolysis

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Reciprocal ST segment depression is commonly found in acute myocardial infarction but its significance remains controversial and it does not usually influence management strategies. When reciprocal ST depression occurs during predischARGE exercise testing, however, it may lead to referral for further investigation, though whether it represents remote ischaemia has not been established. We have prospectively studied 153 patients with acute myocardial infarction treated by thrombolysis within 12 hours of the onset of chest pain. All underwent early exercise testing and 98 also had coronary arteriography. Reciprocal ST depression on the presenting electrocardiogram was found in 67% of patients and was strongly associated with the time from onset of chest pain; those with reciprocal change presenting significantly earlier than those without (3.4 (0.2) v 5.3 (0.4) hours, $p < 0.001$). Importantly there

was no relation between reciprocal change and multivessel disease or patterns of regional wall motion abnormality. During predischARGE exercise testing, reciprocal ST depression occurred in 15% of patients, and isolated ST elevation and depression occurred in 12% and 30%, respectively. Patients with reciprocal ST depression all had Q wave infarcts, and were more likely to have persistent occlusion of the infarct related artery (48% v 27%, $p < 0.05$), and either akinetic or dyskinetic regional left ventricular wall motion (71% v 42%, $p < 0.01$). Importantly, there was no association between reciprocal ST change on the exercise electrocardiogram and multivessel disease.

Reciprocal ST depression in acute myocardial infarction is a passive electrical phenomenon and not a sign of multivessel disease. When it occurs on the presenting electrocardiogram it usually reflects very recent coronary occlusion, being uncommon in patients who present late. Reciprocal change on the predischARGE exercise electrocardiogram reflects extensive Q wave infarction and is not an indication for tertiary referral.

Neurohumoral activation after acute myocardial infarction: differences between the systems and with different drug treatment

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Acute myocardial infarction has been shown to be associated with activation of several neurohumoral systems. The integrated response of these systems at rest and during exercise is less well documented. In this study we have compared plasma noradrenaline, atrial natriuretic peptide, and plasma renin activity in a group of patients who had recently suffered a myocardial infarction with a group of normal control subjects.

Forty eight patients (five women), mean (SEM) age 57.5 (1.3), were studied 18 (0.8) days from a Q wave myocardial infarction, together with nine normal subjects aged 54.2 (2.8). Noradrenaline, atrial natriuretic peptide and plasma renin activity were measured at rest, at submaximal, and symptom limited treadmill exercise. Atrial natriuretic peptide was significantly higher at rest ($p < 0.005$) and during exercise ($p < 0.02$) in the patients compared with the normal people. In the patients ($n = 21$) taking prophylactic β blockers, values were the same as in the other patients at rest, but were higher (368.7 (64.2) v 158.2 (23.8) pg/ml $p < 0.005$) than at symptom limited exercise. Plasma renin activity was no different between the patients and controls at rest or during exercise. Not surprisingly those patients taking diuretics ($n = 10$) had higher values at rest (2.85 (0.6) v 0.98 (0.18) ng/ml/h $p < 0.001$) and during exercise (4.36 (0.89) v 1.68 (0.32) ng/ml/h $p < 0.001$) compared with the remaining patients. Noradrenaline concentration was no different between the patients and the controls either at rest or during exercise. The patients taking diuretics did, however, have higher concentrations than the controls at submaximal exercise (1285 (247) v 632 (72) pg/ml at stage 1 and 1044 (105) v 693 (95) pg/ml at stage 3 of the exercise protocol (both $p < 0.05$). Patients on diuretics had higher resting concentrations than the remaining patients at rest (933 (114) v 650 (42) pg/ml , $p < 0.01$) but not during exercise.

The neurohumoral response to acute myocardial

infarction was largely resolved, both at rest and during exercise, 18 days after acute myocardial infarction, β blockers caused an unexpected increase in atrial natriuretic peptide during exercise without affecting the other hormones. Those patients taking diuretics had, not surprisingly, increased concentrations of plasma renin activity and noradrenaline.

Contrasting effects of isoprenaline and calcitonin gene related peptide on intracellular free calcium concentrations in isolated depolarised cardiac myocytes

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Initial events in ischaemic injury to the myocardium include cellular depolarisation causing intracellular sodium and calcium overload. Calcium overloaded cells exhibit after-depolarisations and after-contractions, which enhance the conditions for abnormal ventricular rhythms. Ultimately cellular calcium overload results in irreversible changes in cellular metabolism and cell death. A study of the regulation of intracellular calcium is therefore important for the prevention of ischaemic cellular injury and arrhythmias. We have examined the effect of isoprenaline and calcitonin gene related peptide (CGRP) upon intracellular free calcium concentrations ($[Ca^{2+}]_i$) in partially depolarised calcium overloaded single cardiac myocytes. Isolated myocytes were prepared by enzymatic digestion and studied in an external solution of composition (mM) NaCl 112, $NaHCO_3$ 24, NaH_2PO_4 1, KCl 5.4, $MgCl_2$ 1, HEPES 5, glucose 10; pH 7.4 with NaOH. Cells were loaded with the esterified form of the calcium sensitive fluorescent dye fura 2/AM and $[Ca^{2+}]_i$ was measured by dual excitation microspectrofluorimetry. Depolarisation of the cell with KCl to a final concentration of 5 to 20 mM resulted in a rise in the $[Ca^{2+}]_i$ that rose to a peak and fell in an exponential fashion. Addition of isoprenaline (1 μ M) during the phase of decline in $[Ca^{2+}]_i$ led to a further decrease in 11 cells studied. ($[Ca^{2+}]_i$ in nM (SEM): baseline, 124.1 (20.2); peak after KCl, 287.5 (42.5); before addition of isoprenaline 202.0 (27.5); after isoprenaline 167.9 (28.8) ($p < 0.05$). By contrast, the addition of CGRP (1 μ M) resulted in a rise in $[Ca^{2+}]_i$ ($[Ca^{2+}]_i$ in nM (SEM): baseline, 175.3 (41.8); peak after KCl, 608.1 (145.3); before addition of CGRP, 302.8 (81.5); after CGRP 473.5 (90.7) ($p < 0.001$)). The p values represent *t* tests for $[Ca^{2+}]_i$ before and after isoprenaline or CGRP.

Although both receptor complexes are linked to the cyclic adenosine nucleophosphate system, isoprenaline and CGRP have differing effects on $[Ca^{2+}]_i$ handling in depolarised, calcium overloaded myocytes.

QT dynamics in patients with left ventricular hypertrophy and heart failure

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In patients with heart failure, ventricular arrhythmias may be more common at lower (near normal) heart rates. The QT interval, which alters with heart rate, reflects cellular

processes that in turn may be important in arrhythmogenesis. We have therefore investigated the rate dependence of the QT interval in 25 patients with stable congestive heart failure (CHF), 12 patients with left ventricular hypertrophy (LVH) and normal systolic function, and seven control subjects. In all subjects QRS duration was normal and none showed evidence of inducible ischaemia. Patient characteristics were: CHF, left ventricular ejection fraction (LVEF) mean (SEM) 29 (4)%, LV wall thickness 1.1 (0.1) cm; LVH, LVEF 58 (8)%, LV wall thickness 1.3 (0.1) cm; controls, LVEF 61 (2)%, LV wall thickness 0.9 (0.1) cm. Twenty-four hour electrocardiographic recordings were obtained within two weeks of the exercise test. On the study day autonomic tests for baroreflex sensitivity, standard deviation of 128 RR intervals, and venous catecholamine concentrations were measured with the subject lying supine. Subjects were then exercised to exhaustion on an upright bicycle ergometer in four minute, 25 watt stages. A 12 lead electrocardiographic record was taken every minute at 50 mm/s, 20 mm/mV. QT Interval was measured in standard lead II during the last 90 s of each stage. Resting heart rate was 72 (4) beats/min in controls, 66 (4) beats/min in LVH, 83 (4) beats/min in CHF ($p < 0.01$, unpaired *t* test, for failure *v* control or LVH). Resting QT interval was 389 (9) ms in controls, 403 (11) ms in LVH, 414 (15) ms in CHF. Bazett's formula corrects these values to 424 (10) ms in controls, 420 (6) ms in LVH, 481 (14) ms in CHF ($p < 0.01$ for CHF *v* control or LVH). Peak heart rate was 127 (8) in controls, 133 (7) in LVH, and 127 (5) in CHF, with QT values of 305 (8), 294 (12), and 316 (12) respectively. The steady state QT/heart rate slope, measured using least squares linear regression, was 1.62 (0.09), 1.67 (0.13), and 2.38 (0.16) ms/beats/min respectively ($p < 0.01$ for CHF *v* either hypertrophy or failure). Autonomic abnormalities and 24 hour tape findings did not relate to the degree of resting QT interval prolongation or to the increase in QT/heart rate slope steepness.

In heart failure QT interval is increased at rest and decreases more rapidly on exercise. As neither the degree of QT prolongation nor the QT/heart rate slope correlated with autonomic function, we suggest that these abnormalities are secondary to intrinsic changes in the cardiac myocytes in heart failure.

Heart rate and sympathetic contribution to exercise induced QT shortening

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Shortening of QT interval on exercise is related to heart rate and increased sympathetic activity, though the contribution of each is unknown. The relative contributions of heart rate and overall sympathetic activity in patients with dual chamber pacemakers implanted for sino-atrial node disease was investigated. Eight patients were exercised for 10 minutes on a bicycle ergometer at a steady workload to increase their heart rate to approximately 110 beats/min. After a two hour recovery period, they were paced while at rest on the bicycle to the same heart rate. QT intervals and forearm venous noradrenaline were measured at rest, during pacing, and during exercise, all at steady state. Mean heart rate (HR) at rest was 66 (2), on exercise was 112 (3), and on pacing was 107 (4) NS for HR_{pace} *v* $HR_{exercise}$). Uncorrected QT intervals were: QT_{rest} 420 (12) ms, QT_{pace} 366 (16) ms, and $QT_{exercise}$ 325 (14) ms ($p < 0.005$ for

$QT_{\text{exercise}} v QT_{\text{pace}}$). Using linear correction for heart rate, the paced QT interval at the exercise heart rate was 359 (17) ms ($p < 0.02 QT_{\text{exercise}} v QT_{\text{pace}}$). Thus the heart rate contribution to QT shortening was 69 (9)% of total QT shortening. Forearm venous noradrenaline concentration was 543 (94) pmol/l at rest, 571 (99) pmol/l during pacing and 1517 (282) pmol/l at 10 minutes exercise ($p < 0.005$ for exercise v rest). There was little correlation between the exercise induced component of QT shortening and the absolute or relative increase in noradrenaline concentration.

Two thirds of QT shortening on exercise is due to the increase in heart rate: the remaining one third is not closely related to forearm venous noradrenaline.

A novel approach to preoperative prediction of the outcome of coronary revascularisation by positron emission tomography (PET)

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Previous assessment of myocardial viability using positron emission tomography imaging relied on uptake of the glucose analogue, ^{18}F -fluorodeoxyglucose (FDG), in hypoperfused asynergic myocardium. A new method that enables simultaneous assessment of myocardial blood flow and tissue viability by positron emission tomography was developed. This relies on the calculation of the perfusable tissue index (PTI) from analysis of transmission, ^{15}O labelled carbon monoxide (C^{15}O , blood volume), and ^{15}O water (H_2^{15}O) emission data sets. The PTI is defined as the proportion of the myocardium that is perfusable by water and thus represents an index of tissue viability. In this study, preoperative assessment of myocardial viability using PTI was performed in 12 patients undergoing coronary revascularisation. In eight patients, an additional FDG scan was performed after a 75 g oral glucose load. Echocardiography performed three to six days before revascularisation identified 33 segments with abnormal wall motion and 26 control segments. Follow up echocardiography performed three to five months later showed 26/33 segments with improved wall motion (recovery) and 7/33 segments that did not recover (non-recovery). Myocardial blood flow in control regions was 0.97 (0.33) ml/min/g compared with 0.73 (0.18) ml/min/g in the recovery ($p < 0.001 v$ control) and 0.45 (0.11) ml/min/g in the non-recovery ($p < 0.001 v$ control) groups. The PTI in the recovery group was > 0.7 in all cases and was slightly less than in the control regions (0.99 (0.15) v 1.10 (0.15), $p < 0.02$). Uptake of FDG in these segments was 92 (17)% ($n = 13$) of the control value. In the non-recovery group, PTI was 0.62 (0.06) ($p < 0.02 v$ control) and always < 0.7 . This was associated with significantly reduced uptake of FDG in the one case where PTI and FDG were compared. This study shows the concordance between the PTI and FDG techniques and suggests that at least 70% of the myocardium should be perfusable by water (PTI > 0.7) to enable contractile recovery.

Our preliminary findings show PTI to be a good predictor of contractile recovery and suggest that myocardial viability may be assessed without metabolic imaging.

Measurement of myocardial perfusion in humans by ultrafast x ray computed tomography: validation by comparison with adenosine thallium tomography

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Ultrafast computerised tomography can be used to evaluate myocardial perfusion in dogs by applying first pass distribution indicator dilution principles. The technique has not previously been validated in humans. Seventy nine myocardial segments from five patients (all male, age 38 to 79) with coronary artery disease documented by angiography or myocardial infarction, or both were investigated. Myocardial perfusion at rest and during infusion of adenosine was assessed using thallium-201 single photon emission computed tomography and ultrafast computed x ray tomography. The ultrafast computed tomography scanner was set to acquire 6 mm thick tomograms in a single plane aligned roughly in the short axis of the left ventricle, with an exposure time of 100 ms. Radiographic contrast was delivered by mechanical injector into the superior vena cava and 20 images gated to end diastole were timed to acquire a baseline image followed by a series to allow the measurement of myocardial enhancement. The sequence was repeated 3 min after the start of intravenous adenosine infusion (140 $\mu\text{g/kg/min}$). Both thallium and ultrafast computed tomography short axis tomograms were divided into eight segments and the percentage variation of each segment from the mean flow tomogram or scintillation count (thallium) was calculated to give the segmental flow index. The flow indices of the 79 segments measured by the two techniques correlated ($r = 0.7$, slope = 1.2 intercept = -0.2 , $p < 0.05$), the mean difference between the methods was 0.0075 with 95% confidence interval = 0.42. Using the thallium scan to define normal or abnormal flow in a segment, ultrafast computerised tomography agreed in 72 of 79 segments with a sensitivity of detection of abnormally reduced flow of 94% and a specificity of 79% (kappa statistic, $\kappa = 0.7$ indicating good agreement overall).

These data show that ultrafast computerised tomography can be used to assess relative myocardial perfusion in humans, after intravenous administration of radiographic contrast.

Emergency surgical revascularisation performed within 24 hours of failed coronary angioplasty

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Between January 1980 and December 1990, 75 of 1539 patients (4.9%) required emergency surgical revascularisation within 24 hours of elective coronary angioplasty in a single centre with surgical facilities on site. In these cases, emergency surgery was undertaken for clinical deterioration: patients who underwent surgery within 24 hours for simple failure of angioplasty were excluded. After 1983, an operating theatre was not maintained on standby. Of the patients requiring emergency surgery, 57 (76%) were men, mean age 55 (range 29 to 73) and 30 (40%) had had a

previous myocardial infarction. Before angioplasty, 68 (89%) were CCS grade III/IV, 59 (79%) had multivessel disease, and six (8%) had a left ventricular ejection fraction of less than 40%. A mean of 2.1 grafts (range one to five) were performed: the internal mammary was used in only one patient. The operative mortality was 9% and in hospital mortality was 17%. Crash bypass, (the requirement for cardiac massage until bypass was established), was necessary in 19 patients (25%); this was the most important outcome determinant and was more common in those patients with multivessel disease and in women. In 10 of these cases, a vacant operating theatre was unavailable: operation was performed in the catheter or anaesthetic room. Crash bypass patients had an operative mortality of 32% and in hospital mortality of 47%, compared with 2% and 7% respectively for the 56 remaining patients who awaited the next available operating theatre. Postoperative complications included arrhythmias (10), wound (five), renal (four), cerebral (two), and septicemia (two): major complications were invariably fatal in those requiring crash bypass. In survivors, mean time to discharge was similar in both groups (13 days, range 5 to 40 days).

The mortality and morbidity associated with emergency revascularisation is high compared with elective surgery: an 83% survival rate was achieved overall. Fifty three per cent of patients needing immediate crash bypass survived due to the availability of surgical backup on site.

Is the ventilation/perfusion mismatch which contributes to exertional hyperpnoea in chronic heart failure (CHF) dependent on limiting right ventricular (RV) output?

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In chronic heart failure, slope m of the exercise relation of minute ventilation/ CO_2 production (VE/VCO_2) is increased when exercise capacity is reduced to peak oxygen consumption ($\text{VO}_{2\text{max}}$) < 20 ml/min/kg, with peak VCO_2/VO_2 (RER_{max}) > 1. We investigated whether the ventilation/perfusion (V/Q) mismatch underlying increased m might be attributable to limitation of right ventricular output and total pulmonary perfusion. In study I, of 42 patients (31 men, age 60 (SD8), drugs withdrawn) with coronary artery disease, positive exercise test, and angiographically normal resting left ventricular function, the 12 patients with exercise tolerance reduced to $\text{VO}_{2\text{max}}$ < 20 ml/min/kg and RER_{max} > 1 had the same m as 30 patients with $\text{VO}_{2\text{max}}$ > 20 ml/min/kg and 15 normal people (29 (5), 30 (6), 26 (5)). Thus m was not increased where, by inference, the exercise induced increase in left ventricular (and thus right ventricular) output was impaired acutely. In study II the exercise induced increase in cardiac output was altered acutely in 13 pacemaker dependent patients by setting the pacemaker (in random order) at 50 beats/min fixed rate (VVI) or in rate-responsive mode (RRM) (which increased exercise heart rate by 51 (7) beats/min). Seven patients (group A) had normal resting left ventricular function (ejection fraction > 50%); six patients (group B) had resting left ventricular dysfunction of mixed aetiology (ejection fraction < 40%). Exercise duration and $\text{VO}_{2\text{max}}$ were lower during VVI than RRM in both groups (group A: $\text{VO}_{2\text{max}}$ 16.9 (0.9) v 20.1 (1.5) ml/min/kg ($p < 0.05$); group B: 13.1 (2.3) v 16.1 (3.4) ml/min/kg ($p < 0.05$). Abolishing the

exertional increase in heart rate during VVI did not alter m in group A (31 (2) to 32 (1)) but increased m in group B (39 (5) to 51 (7) ($p < 0.05$)); thus m can be acutely altered in chronic heart failure.

V/Q mismatch underlying the ventilatory response to exercise may reflect limitation of right ventricular output but only where resting left ventricular function is impaired, as in chronic heart failure.

Cardiac catheterisation in a consecutive series of young patients with first myocardial infarction: should all patients be investigated?

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After myocardial infarction, there is no established policy of who should undergo angiography. We have performed a study to see if postinfarction angina, or abnormal treadmill exercise, or both allows for appropriate decision making. A consecutive series of 186 patients (143 men) under 60 who were discharged from the coronary care unit with a first acute myocardial infarction (standard World Health Organisation criteria) were electively readmitted at a mean (SD) of 60 (31) days for symptom limited exercise testing (Bruce protocol) and cardiac catheterisation. Angina was assessed with a Rose questionnaire; 135 received thrombolysis. A further five patients died unexpectedly before investigation. Significant coronary artery disease was defined as stenosis of one of the three main coronary arteries of > 50%. An exercise test was positive if > 1 mm ST depression occurred at 80 ms past the J point, and negative without ST depression if > 85% of the target heart rate had been achieved. Cine angiograms and exercise tests were reviewed independently by two observers and disagreements settled by a third. Follow up was to death, angioplasty, or bypass surgery. Single vessel disease or normal coronary arteries were present in 97, two or three vessel disease in 83, and left main stem disease in six. The sensitivity and specificity of exercise testing for detecting multivessel disease were 52% and 79% respectively. Of 50% patients with a negative exercise test and no angina only two had three vessel disease, 14 had two vessel disease and 34 had single or no significant disease. None of these 50 was referred for intervention, and none has died over a mean (SD) follow up of 12 (4) months. Of the six patients with left main stem disease all had exercise test times over six minutes and five had positive exercise tests; the sixth had left bundle branch block.

The young patient with a first myocardial infarction who does not have angina and who has a negative exercise test does not require cardiac catheterisation.

Exercise tolerance in angina is improved by Mivazerol (an α_2 adrenoceptor agonist)

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Many patients with chronic stable angina remain symptomatic despite maximal medical treatment or are unable to

tolerate one or more of the triumvirate of β -blockers, calcium antagonists, and nitrates. Mivazerol is a new compound with agonist properties at the α_2 adrenoceptor and has been shown to be an effective antianginal drug in humans when given intravenously. This is the first report of its benefit in an orally administered form. Twelve patients with chronic stable angina and angiographically proved coronary heart disease entered a double blind, placebo controlled, randomised crossover study. Regular antianginal medication was withdrawn for 96 hours, and three ascending doses of mivazerol were compared with placebo using a standard Bruce protocol. All doses of mivazerol increased the total exercise duration, the time to onset of angina, and the time taken to develop 1 mm of ST segment depression. In order of increasing dose (800, 1200, 1600 μ g) the improvement in exercise duration was 11% ($p < 0.05$), 20% ($p < 0.05$), and 24% ($p < 0.01$), in the time to onset of angina 3% (NS), 11% (0.05), and 30% ($p < 0.01$), and in the time to 1 mm ST depression 33% ($p < 0.05$), 43% ($p < 0.01$), and 53% ($p < 0.01$). The heart rate at peak exercise tended to be lower by 3%, 4%, and 3% (all NS). The systolic blood pressure attained at maximal exercise was lower by 11% ($p < 0.01$), 15% ($p < 0.01$), and 14% ($p < 0.01$) respectively.

Mivazerol significantly improved total treadmill exercise duration, the time to onset of angina, and the time to 1 mm ST depression in patients with chronic stable angina. This was associated with an attenuated rise in systolic blood pressure. Mivazerol is an α_2 adrenoceptor agonist and its mechanism of action may be different from that of the classic antianginal drugs.

Are 50% of hypercholesterolaemic patients receiving lipid lowering drug therapy unnecessarily?

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We initiated a trial of lipid lowering drug treatment for hypercholesterolaemia. The present study investigates an unexpectedly high (50%) dropout rate during the dietary stabilisation phase of the trial. Twenty men and women with primary hypercholesterolaemia were entered into the dietary stabilisation phase. All had received dietary advice before the study and were considered to be on a low cholesterol diet. Over three months they were seen four times by the dietician and again advised on diet. This advice was reinforced if patients showed poor compliance as judged by the food record rating scoring system. Patients completed a diary card aiming to score less than 15, thereby ensuring active patient participation. Plasma lipids were measured at the beginning and end of the dietary phase. Ten patients progressed into the active drug treatment phase with persistently raised cholesterol, 10 were withdrawn because of a mean fall in plasma cholesterol concentration from 7.91 mmol/l (range 6.90 to 9.86) to 5.74 mmol/l (range 4.60 to 6.40), $p < 0.001$. Despite previous advice, in 50% of our population cholesterol concentrations fell to near normal with more disciplined supervision.

We believe that dietary treatment in the United Kingdom is inadequately supervised. Lipid lowering drugs are given without a thorough trial of diet with obvious cost implications and unnecessary drug prescription.

Release and metabolism of the novel cardiac hormone, brain natriuretic peptide, in humans

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Brain natriuretic peptide (BNP) was first isolated from the porcine brain. Subsequent studies have shown that BNP is a cardiac hormone synthesised and secreted in the heart and constitutes, together with atrial natriuretic peptide (ANP), a natriuretic peptide family involved in cardiovascular homeostasis. We have recently conducted four studies examining the release and metabolism of BNP in humans. In the first study, we examined the effect of changes in salt intake on plasma BNP concentrations in healthy volunteers ($n = 11$, age 20 to 23). Plasma BNP concentration (mean (SE)) rose significantly on high salt intake, from 1.3 (0.2) pmol/l to 2.0 (0.1) pmol/l ($p < 0.05$). To elucidate further the release of BNP in humans, we examined the effect of fluid removal by haemodialysis on plasma BNP concentrations in volume overloaded dialysis dependent patients with chronic renal failure ($n = 10$, age 16 to 73). The fall in plasma BNP concentration from 21.0 (3.8) pmol/l to 18.1 (3.2) pmol/l correlated strongly with weight reduction after haemodialysis ($r^2 = 0.64$, $p < 0.01$). The last two studies examined BNP clearance in congestive heart failure patients ($n = 7$) who have raised plasma BNP concentrations. 200 mg Candoxatril, an endopeptidase 24.11 inhibitor, increased plasma BNP concentrations from 15.2 (4.4) pmol/l to 24.4 (7.4) pmol/l ($p < 0.05$). Infusion of a large dose of ANP, however, which saturates the ANP clearance receptors did not alter BNP concentrations.

Like ANP, BNP is sensitive to changes in salt and volume in humans. In congestive heart failure patients there is a role for neutral endopeptidase but not for ANP clearance receptors in the metabolism of BNP.

Effects of hormone replacement on lipid and lipoprotein cardiovascular risk markers in postmenopausal women

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Hormone replacement therapy results in a pronounced decrease in incidence of cardiovascular disease in postmenopausal women. Current hormone replacement therapy regimens combine a progestin with oestrogen. To study the effects of hormone replacement therapy on serum lipids and lipoproteins, we randomly allocated 60 healthy postmenopausal women to either oral (continuous conjugated equine oestrogens (0.625 mg daily) with sequential di norgestrel (0.15 mg daily)) or transdermal (continuous oestradiol-17 β (0.05 mg daily)) with sequential norethisterone acetate (0.25 mg daily) hormone replacement therapy. An untreated reference group of 29 women were recruited concurrently. Fasting blood samples were taken basally, at three and six months, and at six monthly intervals thereafter throughout the three year study. Compliance was monitored by recording bleeding patterns and by serum gonadotrophin and gonadal steroid measurements.

Changes in lipids and lipoproteins were seen at three months, and were maximal by six months. These changes persisted throughout the three years. In both treatment groups, we found a significant decline in total cholesterol and low density lipoprotein cholesterol concentrations. These changes were accompanied by similar changes in concentrations of apolipoprotein B. Concentrations of high density lipoprotein cholesterol and apolipoprotein A1 also declined in the combined phase of treatment, due to a decrease in high density lipoprotein subfraction 3. No consistent pattern of change in concentrations of high density lipoprotein subfraction 2 was found with either treatment. Triglyceride concentrations were raised during the oestrogen alone phase of oral treatment, but were reduced during this phase of the transdermal treatment. Addition of progestin lowered triglycerides with both treatments.

Hormone replacement therapy brings about beneficial changes in lipids and lipoproteins irrespective of the route of administration. Such changes may in part explain the reduction in incidence of coronary artery disease in postmenopausal users of hormone replacement therapy.

Intense inhibition of angiotensin converting enzyme (ACE) enhances frusemide induced diuresis during chronic ACE inhibitor therapy

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Short-term angiotensin converting enzyme (ACE) inhibition in heart failure reduces the diuretic response to frusemide. The interaction of diuretics and ACE inhibitors long-term has not been studied. Seven patients with heart failure treated with diuretics (mean dose 91 mg frusemide) and ACE inhibitors (captopril 12.5 mg three times daily) for at least three months were studied. Sodium intake was fixed for three days before study. Usual medication was withheld on study days. Frusemide was given by hourly bolus in identical fashion on each of two study days (mean total for the four hours was 15 mg) to maintain a moderate constant diuresis. Para amino hippurate and inulin were infused to calculate renal plasma flow and glomerular filtration rate (GFR). The patient was asked to void urine hourly for four hours. Captopril (12.5 mg) or matching placebo was given in random order 10 minutes before the end of the first urine collection. Plasma electrolytes and angiotensin II (A-II) were measured hourly. Captopril reduced plasma A-II one hour after dosing. Urine volume increased following captopril, most noticeably in the second hour after dosing (240 (83) to 313 (99) ml/hour; $p < 0.01$). Systolic blood pressure fell (131 (31) to 122 (29) mm Hg; $p < 0.01$) and diastolic blood pressure likewise (74 (15) to 67 (13) mm Hg; $p < 0.01$) but heart rate and GFR were unchanged two hours after the dose. Urinary electrolyte concentrations fell after captopril suggesting increased free water clearance, but urinary sodium excretion (22 (7) to 29 (12) mmol/h; $p < 0.01$) and sodium:creatinine ratio, a measure of fractional excretion of sodium (64 (27) to 77 (36) mmol/ μ mol; $p < 0.01$) increased. The ratio of sodium to phosphate, potassium, and magnesium excretion all increased suggesting that neither proximal nor distal tubular effects accounted for the increase in sodium excretion.

Intensive treatment with ACE inhibitors to maximally suppress A-II formation enhances the natriuretic and aquaretic response to frusemide.

Selective inhibitors of protein kinase C are potent inhibitors of vascular smooth muscle proliferation

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Inhibition of vascular smooth muscle cell proliferation is a possible therapeutic strategy for angioplasty restenosis, vein graft occlusion, and atherosclerosis. As vascular smooth muscle cell proliferation may require activation of protein kinase C, we investigated the effects of inhibitors of protein C on proliferation. We studied the novel staurosporine derivatives Ro 31-8220 and Ro 31-7549, which show 100 fold selectivity for protein kinase C over other protein kinases. Proliferation of first passage rabbit aortic smooth muscle cells was quantified by incorporation of thymidine into DNA and cell viability by measurements of ATP concentration. Cells were rendered quiescent by culture for 72 hours in serum free medium and then stimulated with medium containing 1 μ Ci/ml of 3 H-thymidine and (a) 5% fetal calf serum, (b) a combination of 10 μ M serotonin and 20 ng/ml of platelet derived growth factor (recombinant BB dimer), or (c) 0.1 μ M of the protein kinase C activator, phorbol dibutyrate, which stimulated proliferation by (mean (SE) (n)) 65 (14) (7), 5 (1) (4), 4 (1) (4) respectively (all $p < 0.001$). Proliferation to the three stimuli was inhibited by 10 μ M Ro 31-8220 to 0.5 (0.2) (7), 9 (4) (2), and 5 (1) (4)% respectively, of proliferation rates in the absence of inhibitor (all $p < 0.001$), without any effect on cell viability measured by ATP concentration (110 (2), 120 (10), and 110 (20)% of values in the absence of inhibitor, all NS). Similar effects on proliferation were obtained with 10 μ M Ro 31-7549 (data not given). The concentrations of Ro 31-8220 and Ro 31-7549 that gave 50% inhibition of proliferation to serum (1.7 (0.4) (3) μ M and 5 (1) (3) μ M) were similar, although slightly higher, than those to phorbol dibutyrate (0.7 (0.1) (2) μ M and 1.1 (0.5) (2) μ M).

The data show that Ro 31-8220 and Ro 31-7549 are highly potent inhibitors of vascular smooth muscle cell. They imply, furthermore, that protein Kinase C activation is essential for proliferation responses to serum and serotonin plus platelet derived growth factor.

A comparative study of risk factors for coronary artery disease in south Asian and white people

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Diffuse coronary artery disease (CAD) is a striking cause of mortality and morbidity amongst immigrants from the Indian subcontinent (south Asians). In a case control study we investigated 228 men, mean age (range) 54 (34 to 68). Patients (62 Asian and 52 white people) were studied at least six months after any acute event and had angiographically documented coronary artery disease or electrocardiographic evidence of myocardial infarction. The age matched controls (62 Asian and 52 white) were selected randomly from the patients' general practitioner lists. There was a significant Asian *v* white difference for mean values of insulin (18.6 *v* 12.2 iu/l, $p < 0.001$) and cholesterol concentrations (5.32 *v* 5.87 mmol/l $p = 0.001$); platelet volume (9.16 *v* 8.81

fl $p = 0.008$); white blood cell count ($7.78 \pm 6.96 \times 10^9/l$, $p = 0.002$); occlusion stimulated fibrinolytic activity (101 ± 137 mm, $p < 0.001$); systolic blood pressure (120 ± 130 mm Hg, $p < 0.001$), and diastolic blood pressure (78 ± 82 mm Hg, $p = 0.007$). There was a significant patient *v* control difference in mean values for insulin (18.2 ± 13.9 iu/l, $p = 0.013$); cholesterol (6.01 ± 5.25 mmol/l, $p < 0.001$); triglyceride (3.11 ± 1.98 mmol/l, $p = 0.001$); ApoB100 (83.2 ± 75.3 mg/dl, $p < 0.001$); ApoA1 (117.0 ± 128.6 mg/dl, $p < 0.001$); and Lp (a) concentrations (30.9 ± 7.4 mg/dl, $p < 0.001$); body mass index (26.1 ± 25.1 , $p = 0.036$); body fat ($22.1 \pm 20.7\%$, $p = 0.029$); and fibrinogen (2.29 ± 2.11 g/l, $p = 0.032$); factor VII ($135 \pm 167\%$, $p = 0.014$); platelet ($274 \pm 238 \times 10^9/l$, $p = 0.001$); β -thromboglobulin (48.7 ± 30.4 iu/ml, $p < 0.001$), and platelet factor 4 (12.1 ± 5.8 iu/ml, $p < 0.001$) concentrations. A history of diabetes was more common in south Asians than in white people ($21\% \pm 6\%$) and reported hypertension more common among white people ($25\% \pm 35\%$). Smoking habits were roughly equal ($87\% \pm 89\%$). In south Asians a metabolic state of hyperinsulinaemia and diabetes mellitus may be responsible for their high incidence of coronary artery disease, but the decreased fibrinolytic capacity, the higher white blood cell count and the larger platelets may also be important contributory factors.

Whereas this study can only consider survivors, it is likely that these factors will also be risk factors for coronary artery disease.

Insulin, alcohol, and the risk of cardiovascular disease in middle aged men

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Because the mechanisms underlying the alcohol cardiovascular disease relation are unclear, we studied the relation between alcohol consumption and fasting plasma insulin and lipoprotein concentrations in a stratified random sample of 824 men aged 40 to 69 who attended a health survey in east Bristol. Light to moderate drinkers (> 5 – 40 g alcohol/day), compared with non or occasional drinkers (0 – 5 g alcohol/day), had lower plasma insulin concentration by 13% or 1.0 mU/l, lower cholesterol concentration by 4% or 0.2 mmol/l, and lower total cholesterol: HDL cholesterol ratio by 7% or 0.4 , but higher total high density lipoprotein cholesterol concentration by 7% or 0.08 mmol/l and higher high density lipoprotein₃ cholesterol concentration by 8% or 0.06 mmol/l. Conversely, heavy drinkers (> 40 g/day) compared with light to moderate drinkers, had higher plasma insulin concentration by 19% or 1.3 mU/l and higher total high density lipoprotein cholesterol concentration by 11% or 0.13 mmol/l but lower total cholesterol: high density lipoprotein cholesterol ratio by 8% or 0.4 . All these differences were statistically significant and were shown to be independent of body mass index and smoking habits by multiple regression analysis and one way analysis of variance (Ancover).

The U shaped relation between plasma insulin and alcohol consumption might explain some of the decrease in coronary heart disease among moderate drinkers and the increase in hypertension among heavy drinkers.

Linoleic acid and the risk of sudden cardiac death

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An inverse relation between the essential fatty acid linoleic acid and the risk of angina pectoris and acute myocardial infarction in men has already been shown. We therefore investigated in a population case control study whether linoleic acid was related to the risk of coronary heart disease presenting as sudden cardiac death. The relative amount of linoleic acid was measured in adipose tissue as a marker of long term dietary intake of this fatty acid. Sixty five cases of sudden cardiac death occurring in men under the age of 65 with no history of coronary heart disease were identified from the City of Southampton. Subcutaneous adipose tissue was sampled from the abdomen at post mortem and stored at -70°C . Two hundred and thirty six living healthy age and sex matched controls, with no history of coronary heart disease, were drawn from general practices in which sudden cardiac death cases were registered, and a needle biopsy of adipose tissue was sampled from the same site under local anaesthetic and stored in the same way. The proportionate storage of linoleic acid in adipose tissue was measured by gas liquid chromatography with the laboratory blind to the state of adipose tissue samples.

The estimated relative risk of sudden cardiac death was 4.6 (95% confidence interval 1.61 – 13.1) when comparing the lowest quintile of adipose tissue:linoleic acid distribution in the controls with the top quintile. This inverse relation between linoleic acid and risk of sudden cardiac death is further evidence that a lower intake of this essential fatty acid increases the risk of coronary heart disease.

Assessment of the prevalence of coronary heart disease (CHD) in south Asians: difficulties with conventional methods

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A random population survey was carried out to detect the presence of coronary heart disease in south Asians who form 85% of the residents in a ward of Southall. A total of 375 patients (193 men and 182 women) age range 30 to 64 participated. A history of angina and myocardial infarction was obtained, and the Rose questionnaire was administered by an interviewer who spoke the patient's language. A cardiologist also obtained an independent history. The resting electrocardiogram was analysed using the Minnesota code for Q/QS patterns, and for ischaemia according to criteria specified in the Whitehall Study. Angina was detected by history in 2.6% men and 2.2% women, by Rose questionnaire in 4.7% men and 4.9% women, and by a cardiologist in 4.1% men and 0.6% women. A history of myocardial infarction was detected by history in 4.1% men and no women, by Rose questionnaire in 5.2% men and 2.2% women and by a cardiologist in 4.1% men and 0.5% women. Q/QS codes were present in 1.6% men and 0.6% women whereas 12.4% men and 13.7% women satisfied the criteria for ischaemia. In men there was significant

correlation between history and cardiologist for a diagnosis of myocardial infarction ($p < 0.001$), and borderline significance for a diagnosis of angina ($p = 0.07$), but no significant correlations for myocardial infarction or angina between the Rose questionnaire and history or cardiologist. There were no correlations in women for myocardial infarction or angina between Rose questionnaire, history, and cardiologist. The rates of Q/QS codes were similar to known values for the British population (Whitehall and Scottish Heart studies) whereas ischaemic electrocardiographic abnormalities had higher rates in both south Asian men and women. Such abnormalities occurred in predominantly asymptomatic persons. These findings suggest that the administered Rose questionnaire, originally validated in white men, needs to be used with caution in south Asians, and especially women when assessing prevalence of coronary heart disease.

If ischaemic electrographic criteria based on ST-T abnormalities are to be used for assessment of prevalence of coronary heart disease in ethnic groups and particularly in women then further validation is necessary.

Prevalence of coronary heart disease in south Asians living in west London is not higher than in the English population

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Although standardised mortality ratios (SMRs) suggest a 36% higher mortality from coronary heart disease in south Asians living in London compared with the native population, there are no comparative data on the prevalence of coronary heart disease in south Asians. To determine the prevalence of overt coronary heart disease in south Asians, a random selection of case notes and appropriate hospital records of two general practices with a predominantly south Asian population were studied and compared with a third practice, within two miles of the others and serving a similar social group but predominantly English population. Patients who had documented myocardial infarction, positive coronary angiography, cardiac surgery, or cardiac chest pain (supported by investigations) were regarded as having overt coronary heart disease. The notes of 1510 south Asian 30 to 64 year old men were examined, giving 45 cases of overt coronary heart disease, a prevalence of 3.0% (95% CI 2.1–3.8). For 1176 English men of similar age 34 cases of overt coronary heart disease were identified, a prevalence of 2.9% (1.9–3.9). The prevalence within different age bands was as follows for Asians *v* English: 30–39, 0.9% (0.33–2.02) *v* 0.2% (0.01–1.35); 40 to 49, 1.7% (0.70–3.59) *v* 1.7% (0.62–3.69); 50 to 59, 6.1% (3.85–9.12) *v* 5.2% (3.25–9.34); 60 to 64, 10.1% (5.28–18.89) *v* 10.0% (5.28–16.86). Different Asian subpopulations showed different prevalence rates—namely, Moslem 4.7% (3.13–6.63), Sikh 2.0% (1.03–3.48) ($p = 0.008$).

These data show that (a) the prevalence of overt coronary heart disease appears low in south Asians and is similar to that of the English. (b) Differences exist within Asian subpopulations.

Factors influencing the use of thrombolytic therapy in six district general hospitals

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A prospective audit of time delays in the admission of patients with acute myocardial infarction (AMI) and the utilisation of thrombolysis was performed in six district hospitals. Of 1746 patients admitted with possible AMI, and for whom accurate timing of the onset of symptoms is available, 1341 (77%) arrived at hospital within six hours. Further arrivals over the next six hours increased the total to 1560 (89%), an hourly increment of only 2%. Of 1069 patients with a final diagnosis of definite AMI, 44% received thrombolysis within six hours of onset of symptoms and 59% within 24 hours. A contraindication was stated in 398 (37%), whereas 43 (4%) had no stated contraindication to thrombolysis nor did they receive it. Most contraindications, based on a final diagnosis of AMI, fell into four groups: diagnosis uncertain 73/398 (18.3%); non-qualifying electrocardiogram 81/398 (20.3%); too late 79/398 (19.8%), and other 89/398 (22.4%). "Other" was a contraindication that required an explanation on the data entry form; in only 4/89 was an explanation provided. "Too late" was a locally determined criterion influenced partly by participation in trials of late thrombolysis. The frequency of use of contraindications varies widely between hospitals (25–47%). "Diagnosis uncertain" and "non-qualifying electrocardiogram" are to some degree subjective, and diagnostic uncertainty appears to be common. Of patients having an admission diagnosis other than definite AMI, that is, probable AMI, unstable angina, chest pain of uncertain cause, 410/1264 (32%, range 23–43%) had a final diagnosis of AMI. By contrast 28/670 (4%) with an admission diagnosis of AMI subsequently had the diagnosis changed. The use of thrombolysis depends on the admission diagnosis; 71% of patients with an admission diagnosis of definite AMI had thrombolysis, whereas 43% of those in whom the diagnosis was changed to one of definite AMI received thrombolysis. Although complete concordance between admission and final diagnosis is not realistic the variation between hospitals suggests that improvement in diagnostic accuracy may be possible.

A substantial reduction in prehospital delays, although desirable, will not greatly increase the total use of thrombolysis within the first six hours after onset of symptoms. The number of patients not receiving thrombolysis because of contraindications varies by a factor of two between hospitals; this may reflect diagnostic uncertainty. More rigorous use of contraindications could increase the use of thrombolysis within hospital.

Tricuspid annular dilatation: an important cause of tricuspid regurgitation after mitral valve replacement

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The development of late tricuspid regurgitation after mitral valve replacement is accompanied by a considerable

reduction in exercise capacity and poor functional outcome. We have attempted to define its pathogenesis more clearly by comparing the clinical and echocardiographic characteristics of two groups of patients, with ($n = 13$) and without ($n = 13$) clinically significant tricuspid regurgitation after mitral valve replacement. The groups were matched for age and sex and were studied at similar intervals postoperatively (mean (SD) 8.5 (4.8) yr *v* 7.3 (2.8) yr; NS). The severity of preoperative symptoms was comparable but current functional state was worse in those with severe tricuspid regurgitation (New York Heart Association III or IV), 6/13 *v* 1/13; $p < 0.01$). Preoperative haemodynamic data were similar but mild tricuspid regurgitation was detected at preoperative palpation only in the group who later developed clinically significant tricuspid regurgitation (5/13 *v* 0/13 ($p < 0.02$)). Current echocardiographic parameters of left ventricular function were similar but right ventricular diameter was greater in those with severe tricuspid regurgitation (4.9 (0.4) cm *v* 4.0 (0.8) cm; $p < 0.01$). None of the patients had evidence of rheumatic tricuspid valve disease but the tricuspid annulus was wider in those with severe tricuspid regurgitation 3.7 (0.5) cm *v* 3.2 (0.4); $p < 0.05$). Prosthetic function was normal in all patients and estimated pulmonary artery systolic pressure was comparable in the two groups (38 (10) mm Hg *v* 30 (14) mm Hg; NS).

These results indicate that late tricuspid regurgitation after mitral valve replacement is related to tricuspid annular dilatation occurring in the absence of pulmonary hypertension. Its detection and correction at the time of initial surgery may lead to a reduction in the prevalence of this important complication of mitral valve replacement.

Effect of retrograde non-transseptal balloon dilatation of the mitral valve on left atrial function in mitral stenosis

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Retrograde non-transseptal balloon dilatation of the mitral valve (RNBMV) for mitral stenosis with a steerable cardiac catheter is a new, effective, and safe technique developed in our institute. It does not involve puncture of the atrial septum, thus being the only technique that allows reliable assessment of left atrial function. Of the 117 patients who underwent RNBMV for mitral stenosis 13 patients (age 48 (11) in sinus rhythm, before and six months after RNBMV were studied. Left atrial volumes (cm^3) were measured echocardiographically at mitral valve opening (maximal, V_{max}), at onset of left atrial systole (P wave of the electrocardiogram, V_{p}), and at mitral valve closure (minimal, V_{min}) from the apical (2) and (4) chamber views using the biplane area length method. Left atrial contractile function was assessed with the left atrial active emptying fraction ($\text{ACTEF} = (V_{\text{p}} - V_{\text{min}})/V_{\text{p}}$). Mitral valve area (MVA, cm^2) was assessed with pulsed Doppler. After RNBMV: MVA (0.83 (0.31) *v* 1.96 (0.37), $p < 0.0001$) and ACTEF increased (0.23 (0.06) *v* 0.29 (0.09), $p < 0.005$), V_{max} decreased (118 (24) vs 83 (14), $p < 0.0001$), and V_{max} was inversely related to MVA ($r = 0.81$).

RNBMV for mitral stenosis reduces left atrial size and improves left atrial contractile function. Reduction of left atrial size is an important indicator of the effectiveness of RNBMV.

Does biplane transoesophageal imaging confer advantages in the assessment of mitral prosthesis function?

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To determine whether biplane transoesophageal (TEE) imaging offers any advantages in the evaluation of mitral prosthetic function when compared with either standard single transverse plane (T-TEE) imaging or the precordial (PE) approach, a series of 43 consecutive patients with suspected prosthetic dysfunction (eight bioprostheses; 35 mechanical) were studied. Clinical indications included suspected transvalve or paravalve leakage (32), endocarditis (five), source of emboli (three), acute valve obstruction (two), mitral annulus rupture (one patient). All had had an earlier PE study. Correlative surgical confirmation of the TEE finding was subsequently available in 15 patients, and catheterisation confirmation in 24/28 of the remainder. Only four patients, all with normal PE and TEE findings, did not undergo correlative studies. Two independent blinded observers reported both the PE and TEE studies comparing information gained from PE imaging, transverse plane TEE, longitudinal plane TEE, and by combining information from both TEE planes. Both PE and TEE suggested eight patients to have normal prosthesis function. In the remaining 35 patients (all with pathological prosthetic function), PE failed to detect the lesion in 28/35 cases. The following lesions were identified by biplane TEE; vegetations or infective sequelae (five), left atrial or prosthetic thrombus (three), acute prosthetic thrombosis (one), mitral annulus rupture with pseudoaneurysm formation (one), prosthetic obstruction due to sub valve pannus (one). In the remaining 25 patients, pathological mitral regurgitation was the only abnormal finding. This was defined by ultrasound criteria as mild (six), moderate (four), and severe (15). In 12 cases the leak was single and paravalvar, in six there were two major paravalvar leaks, in three there were three, in two it was central orifice and in one there was a combination of paravalvar and central orifice leakage. Biplane imaging proved to have many advantages over imaging in either single plane as only it allowed a complete scan of the valve sewing ring. The longitudinal plane (L-TEE) proved optimal for the identification of leaks (L-TEE 17; T-TEE 9) or other pathological lesions sited anteriorly or posteriorly on the valve or around the sewing ring whereas transverse plane was superior at detecting medial or lateral leaks (L-TEE 14; T-TEE 20) or pathology.

Thus imaging in both TEE planes is a prerequisite for a complete mitral prosthesis evaluation.

Magnetic resonance jet velocity mapping validated against Doppler echocardiography in mitral and aortic valve stenosis

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To evaluate the accuracy of magnetic resonance phase shift jet velocity mapping *in vivo*, we used a 0.5 tesla Picker

magnetic resonance machine and a field even echo rephasing sequence with a very short (3.6 ms) echo time to measure peak poststenotic jet velocity in 15 consecutive patients recruited with known valve disease (five mitral stenosis, three of these restudied after balloon dilatation of the mitral valve, and 11 aortic stenosis). On the same day as the magnetic resonance study, these patients underwent Doppler echocardiographic measurement of peak jet velocity by an experienced investigator; both studies were performed blind. In addition, the results of 10 further magnetic resonance investigations of aortic stenosis in patients referred for magnetic resonance imaging were reviewed. In the 15 recruited patients, 18 out of 19 magnetic resonance studies produced velocity maps from which peak jet velocities could be measured, and results showed good agreement with those from Doppler measurement ($r = 0.94$, mean = 3.1 m/s, range: 1.5 to 5.9 m/s, mean of differences = -0.23 m/s, limits of agreement = 0.96 m/s). The poor quality of one velocity map was attributed to misplacement of the imaging slice. Satisfactory magnetic resonance velocity maps were obtained in all of the remaining 10 cases, in two of which, distortion and calcification of the valves rendered accurate Doppler assessment impracticable.

In vivo magnetic resonance peak jet velocity measurements agree well with those made by Doppler ultrasound. The technique is likely to have value for measurement of jet velocity at locations where ultrasonic access is limited.

Pharmacological increase of extracellular magnesium concentrations slows conduction in normal ventricular myocardium independently of stimulation frequency

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Experimental evidence suggests that magnesium salts protect against the development of malignant ventricular arrhythmias during acute myocardial ischaemia by effects on conduction velocity. Although it is now well established that pharmacological elevation of extra-cellular magnesium concentrations in humans has no influence on ventricular refractoriness, the changes in intraventricular conduction have not been formally assessed other than by measurement of paced QRS duration which has produced conflicting results. Accordingly, we studied the effect of intravenous magnesium salts on the conduction time between two right ventricular endocardial sites in eight patients (age 23 to 51) with structurally normal hearts undergoing intracardiac electrophysiological investigations. Signals from a standard multipolar electrode catheter in the right ventricular apex and a monophasic action potential contact electrode catheter in the right ventricular outflow tract were recorded continuously, digitised at 1 kHz and stored on optical disc for subsequent analysis. Constant rate pacing was performed via the multipolar catheter at 500 and 300 ms cycle lengths and the conduction time from the stimulus artefact to monophasic action potential upstroke of the contact electrode was measured before and after administration of intravenous $MgSO_4$ (0.2 mmol/kg). Serum Mg concentration rose from 0.87 (0.04) to 2.31 (0.35) mmol/l ($p < 0.0001$). Paced QRS duration increased from 146 (16) to 152 (19) ms at the 500 ms cycle length ($p < 0.05$) and from 142 (9) to 146 (10) ms at the 300 ms cycle length ($p = 0.06$). The conduction time between the right ventri-

cular sites was prolonged from 54 (11) to 60 (9) ms ($p < 0.01$) and from 55 (11) to 62 (10) ms ($p < 0.001$) at the 500 and 300 ms cycle lengths. There was no significant change in monophasic action potential duration at 50, 70, or 90% repolarisation at either cycle length or in ventricular effective refractory period.

Acute pharmacological increase in extracellular magnesium concentrations slows intraventricular conduction in normal myocardium. This effect seems to be independent of stimulation frequency and is unlikely to involve modulation of fast sodium channels.

Regional thallium-201 washout rate and myocardial hypertrophy in hypertrophic cardiomyopathy: relation to exertional chest pain

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To study the mechanism of exertional chest pain in hypertrophic cardiomyopathy (HCM), we performed dipyridamole loading thallium-201 single photon emission computed tomography in 82 consecutive patients with hypertrophic cardiomyopathy and analysed the three hour washout rate of thallium, in relation to the single photon emission computed tomography image, regional wall thickness on cross sectional echocardiography, and other clinical findings using uni- and multivariate analysis. Twenty five of 82 (31%) patients had a history of exertional chest pain and showed a significantly lower total washout rate and greater maximal left ventricular wall thickness than patients without chest pain (32.0 (10.0)% *v* 37.1 (9.3)%, $p = 0.027$; 26.7 (7.4) mm *v* 22.8 (7.3) mm, $p = 0.031$ respectively). Even in mild or non-hypertrophied areas, patients with chest pain had a significantly lower regional washout rate than patients without pain (32.5 (10.4)% *v* 38.0 (9.4)%, $p = 0.022$) despite similar left ventricular wall thickness (11.5 (2.3) mm *v* 11.4 (2.7) mm, NS). There was a weak correlation of regional washout rate and regional wall thickness in 298 analysed quadrant areas ($r = -0.29$, $p = 0.0001$); the correlation was similar even in severely hypertrophied areas ($r = -0.35$, $p = 0.0015$). Discriminant analysis identified a reduced washout rate, greater maximal left ventricular wall thickness, and supraventricular arrhythmias as the best predictors of exertional chest pain (sensitivity 68%, specificity 64% and accuracy 67%: $p = 0.009$).

These results suggest that exertional chest pain in hypertrophic cardiomyopathy relates to reduced coronary flow reserve, which is a function of the disease process, and not the magnitude of left ventricular hypertrophy.

Repolarisation abnormalities in patients with hypertrophic cardiomyopathy and ventricular arrhythmias: are they important?

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Patients with hypertrophic cardiomyopathy have a high incidence of ventricular arrhythmias. One possible mechanism for these arrhythmias is inhomogeneity of repolarisation secondary to the disorganisation of myo-

cardial architecture seen in this condition. To investigate this mechanism, assessment of ventricular repolarisation was undertaken in 31 patients with hypertrophic cardiomyopathy (mean age 39, 20 men), 14 of whom had documented clinical or inducible ventricular arrhythmias, in an attempt to elucidate possible abnormalities of repolarisation that might provide a substrate for these arrhythmias. Patients with and without arrhythmias were similar in terms of clinical, echocardiographic, and basic electrophysiological features. QT and QTc dispersion was determined by measuring the QT interval and determining the QTc value in each of the 12 leads of a standard electrocardiograph that was enlarged by a factor of four. In addition, all patients underwent electrophysiological study including measurement of dispersion of endocardial monophasic action potential duration from right and left ventricles.

QT and QTc dispersion and monophasic action potential dispersion were also evaluated in a control group with no structural heart disease. QT and QTc dispersion was similar in patients with and without ventricular arrhythmias (QT dispersion 76 (40) ms *v* 64 (11) ms, QTc dispersion 0.08 (0.04) s *v* 0.07 (0.01) s), although overall QT and QTc dispersion were increased as compared with controls (43 (12) ms, $p = 0.001$ and 0.05 (0.02) s, $p = 0.002$ respectively). Monophasic action potential dispersion was increased in the patients with hypertrophic cardiomyopathy (63.6 (39) ms) as compared with controls (26 (5) ms, $p < 0.05$), but again there was no difference in the degree of dispersion between those with and without ventricular arrhythmias.

This study has shown that abnormalities of ventricular repolarisation are present in patients with hypertrophic cardiomyopathy as measured by an increase in QT and QTc dispersion and an increase in monophasic action potential dispersion. This is not associated, however, with the presence of clinical or inducible ventricular arrhythmias. Thus dispersion of repolarisation does not appear to be relevant to the genesis of ventricular arrhythmias in this condition.

Phosphorus-31 magnetic resonance spectroscopy of the failing heart in ischaemic cardiomyopathy, myocarditis, and severe valve disease

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Heart failure is a recognised feature of diseases of the myocardium such as myocarditis, ischaemic cardiomyopathy, and severe aortic and mitral valve disease. Abnormalities in metabolism may underlie the development of decompensated failure and the metabolic changes may be the same regardless of the etiology of the disorder. To examine ATP and phosphate energetics 29 patients were compared with 13 controls using a 1.9 Tesla 60 cm bore magnet. The phase modulated rotating frame imaging technique was used for spectroscopy and cardiac spectra were localised using stacked plots. The phosphocreatine (PCr) and ATP peaks were triangulated and an adjustment for ATP contamination from blood was made. Eighteen patients with symptoms of heart failure (New York Heart Association II–III) and on treatment (fractional shortening 27(10)%; end diastolic dimension; 6.0 (1.0) cm; left ventricular end diastolic pressure, 16.0 (8.0) mm Hg) had a PCr:ATP ratio

of 1.06 (0.38) that was significantly ($p < 0.01$) lower than in controls (1.5 (0.2)) or in the 11 patients with no dyspnoea (fractional shortening, 41 (7.4)%; end diastolic dimension, 5.7 (1.2) cm; left ventricular end diastolic pressure, 11.0 (7.4) mm Hg; PCr:ATP, 1.63 (0.2).

Phorbol ester and adenosine triphosphate potentiate adenylate cyclase activity in endothelial cells

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Interaction between different intracellular second messenger systems ("crosstalk") may modulate the response of a cell to an extracellular stimulus. This phenomenon was investigated in cultured bovine aortic endothelial cells (BAEC). These were pretreated for 30 min in culture with 100 nM phorbol 12-myristate 13-acetate (PMA; an activator of protein kinase C, PKC), 50 μ M adenosine triphosphate (ATP), or culture medium alone and were then washed and harvested. Basal activities, and forskolin (10 μ M), sodium fluoride (NaF, 10 mM), and isoprenaline (10 μ M) stimulated adenylate cyclase activities were measured in BAEC homogenates. Pretreatment with PMA increased basal and stimulated adenylate cyclase activity above control values in a dose dependent manner: basal mean (SEM) 16.8 (1.6) *v* 12.2 (1.2), forskolin 116.0 (9.7) *v* 79.8 (6.0), NaF 104.7 (7.5) *v* 72.2 (5.0), isoprenaline 41.3 (3.3) *v* 34.1 (2.4) pmol cyclic AMP/min/mg protein, $p < 0.01$ for all, $n = 14$. Pretreatment with ATP had a similar effect on adenylate cyclase activity: basal 21.5 (5.7) *v* 19.1 (5.7), forskolin 79.5 (11.4) *v* 62.4 (4.6), NaF 93.3 (17.2) *v* 73.3 (14.2), and isoprenaline 57.8 (8.6) *v* 43.7 (7.0) pmol cyclic AMP/min/mg protein, $p < 0.05$ for all, $n = 5$. Pretreatment of BAEC for 60 min with 100 nM staurosporine, an inhibitor of PKC, abolished the enhancement of adenylate cyclase activity caused by PMA ($p < 0.05$) but had no effect on basal or stimulated adenylate cyclase activity in control or ATP pretreated cells. Neither PMA nor ATP pretreatment caused phosphorylation or the inhibitory guanine nucleotide-binding protein in BAEC ($n = 5$). There was no change in BAEC β adrenoceptor density after PMA pretreatment, measured by 125 I-iodocyanopindolol binding to BAEC membranes. Thus activation of PKC enhanced adenylate cyclase activity in BAEC. Extracellular ATP also enhanced adenylate cyclase activity, but independently of PKC.

Increased adenylate cyclase activity due to activation of PKC indicates the potential for crosstalk between second messenger systems in endothelial cells.

Increased fibrinolytic activity in the intima of atheromatous coronary arteries: protection at a price?

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Internal mammary artery, human saphenous vein, aorta, and coronary endarterectomy specimens from patients undergoing coronary surgery were crushed in polyethylene glycol solution and the supernatant assayed for tissue plas-

minogen activator (tPA) activity (using chromogenic substrate S2251) and protein content. Punch biopsies (2 mm) were taken and incubated on fibrin plates. Diameters of fibrinolysis were (mm (SE)): internal mammary artery ($n = 8$) 7.0 (0.9), saphenous vein ($n = 10$) 4.9 (0.7), and endarterectomy ($n = 11$) 10.4 (1.0). Endarterectomy specimens produced significantly larger areas of fibrinolysis compared with internal mammary artery ($p = 0.03$) and saphenous vein ($p = 0.001$) (Mann-Whitney U test). Extractable tPA activity was (mg tPA/mg protein (SE)): aorta ($n = 7$) 5.1 (0.9), internal mammary artery ($n = 9$) 5.4 (1.7), saphenous vein ($n = 7$) 4.1 (0.2), and coronary endarterectomy ($n = 10$) 27.6 (4.0). Coronary endarterectomy specimens had significantly more tPA activity than all other samples ($p < 0.001$) (Mann-Whitney U test). Antibody to tPA suppressed activity of endarterectomy supernatant. These data show that endarterectomy cores from coronary arteries exhibit greater fibrinolytic activity than normal veins or arteries.

Increased tPA activity in these vessels may help preserve patency but possibly at the expense of intimal instability and fibrous proliferation.

Effects of angiotensin converting enzyme inhibition on tissue renin and angiotensinogen gene expression

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Recent studies have shown the presence of renin and angiotensinogen mRNA in several tissues. To examine the effects of angiotensin converting enzyme inhibition on tissue renin and angiotensinogen gene expression male Wistar rats ($n = 6$, weight 300 to 400 gm) were treated for five days with 1.5 mg/kg/day perindopril administered by gavage. Control rats ($n = 6$) were given the vehicle (water). At the end of the treatment period plasma renin concentration was considerably higher in the perindopril group compared with the controls (317.0 (48.8) ng/ml/h *v* 9.4 (1.3) ng/ml/h) and the angiotensin II concentration significantly lower (< 2.0 pg/ml *v* 11.0 (2.1) pg/ml). Renin and angiotensinogen mRNA concentrations were compared by northern blotting. For internal control, filters were also probed for mRNA and HGPRT. Perindopril treatment led to a greater than fourfold increase in kidney renin mRNA concentration. By contrast no significant differences were seen in renin mRNA concentrations in the brain, heart, adrenal, aorta, testes, and liver of perindopril treated and control rats. Likewise no significant change was found in angiotensinogen mRNA concentrations in any of the tissues of the treated group.

These results therefore indicate qualitative differences in feed back control of renin gene expression in renal and extrarenal tissues. Although tissue renin angiotensin systems may be important targets for the actions of angiotensin converting enzyme inhibitors, their short term administration does not cause significant changes in renin or angiotensinogen mRNA concentrations in several sites.

Detection of proliferating cells in human coronary artery

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Despite the lack of direct evidence, smooth muscle cell proliferation has been implicated in the development of atherosclerotic lesions in humans. To determine the location and degree of cell proliferation, immunohistochemistry with PC-10 antibody was performed on segments of human coronary artery obtained from our transplantation programme. This antibody is directed against the proliferating cell nuclear antigen (PCNA), which is known to accumulate in proliferating cells. Specific cell types were then identified on serial sections for smooth muscle cells (α actin), macrophages (Mac 387), and endothelial cells (Q-Bend 10). PC-10 positive cells were detected predominantly in the neointima and to a lesser extent in the medial layers. An intact endothelium was identified on top of the neointimal layers, which contained an abundance of macrophages and smooth muscle cells in a synthetic phase. Occasional macrophages were also seen in the media. By an established organ culture model the specificity of PC-10 for proliferating cells was then investigated. Segments of human coronary artery were maintained in culture for 14 days, pulse labelled with ^3H thymidine for the last 24 hours, and immunostained for PC-10 before autoradiography. By this double labelling technique it was shown that only a minority of PC-10 positive cells had incorporated ^3H thymidine.

Cell proliferation occurs in diseased human coronary arteries; PC-10, however, overestimates the number of actively dividing cells. This may simply reflect the long half life of PCNA or may be the result of growth factors from the vessel wall causing enhanced synthesis of the PCNA protein.

Electrophysiological assessment and follow up of survivors of cardiac arrest

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Few data are available on the long-term outcome of cardiac arrest survivors in the United Kingdom. Between July 1987 and June 1991, 37 patients were referred for assessment after resuscitation from a cardiac arrest not associated with acute myocardial infarction. The age range of the patients was 19 to 72 (mean 51.7) years. Diagnoses were coronary artery disease in 21 (with previous myocardial infarction in 17), dilated cardiomyopathy in six, valvular heart disease in three (one with concomitant coronary artery disease), Wolff-Parkinson-White syndrome in two, and miscellaneous in four. Twenty four patients had impaired left ventricular function and 16 had left ventricular ejection fractions of $< 30\%$. Twenty five received empirical antiarrhythmic drug treatment before referral and drug toxicity was implicated as a cause of cardiac arrest

in three patients. Electrophysiological studies were performed in thirty five patients. Eighteen (group I) had inducible sustained monomorphic ventricular tachycardia, 15 (group II) had either no arrhythmias or non-specific arrhythmias inducible, and the two patients with Wolff-Parkinson-White syndrome had reciprocating tachycardia and rapidly conducted atrial fibrillation. Of the 18 patients in group I, six have been treated with drugs alone and 12 have had non-pharmacological treatment (implantable cardioverter-defibrillator in seven, surgery in two, percutaneous coronary angioplasty in one, transplant in one, antitachycardia pacemaker in one). Of the 15 patients in group II, three are on no treatment, two have had coronary artery bypass surgery, five have had defibrillators implanted, and five were prescribed anti-arrhythmic drugs. At a mean follow up of 464 (405) days, 32 patients remain alive. The five who have died all had ejection fractions below 30% ($p = 0.01$), four were in group I, and one death was sudden.

With use of electrophysiological studies for risk assessment and treatment selection, many patients will require non-pharmacological treatment to prevent recurrence of cardiac arrest. The main determinant of survival appears to be left ventricular function, and with optimal treatment the risk of sudden death is low.

Efficacy and safety of dofetilide, a new class III antiarrhythmic agent, in recurrent ventricular tachycardia

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Concern about the safety and efficacy of class I anti-arrhythmic drugs has prompted the development of potent new class III agents such as dofetilide, which selectively prolongs action potential duration and refractoriness by blockade of the delayed rectifier potassium current without depressing conduction or contractility. The short-term efficacy of dofetilide was evaluated at four dose levels in 39 patients with recurrent ventricular tachycardia (mean left ventricular ejection fraction 40 (13%) inducible by programmed electrical stimulation (maximum three extra-stimuli, 600 and 400 ms drive cycle lengths and two sites). Programmed stimulation was performed before and after intravenous administration of dofetilide as loading (15 min) and maintenance (45 min) infusions at doses of 1.5, 3.0, 6.0, and 9.0 mcg/kg. At 1.5 mcg/kg, there was no significant change in ventricular refractoriness or QTc and only 1/9 patients was non-inducible at restimulation. Doses of 3.0 to 9.0 mcg/kg all significantly prolonged ventricular effective refractory period (by 9.4 (15.5%) and functional refractory period (by 7.8 (16.6%)) compared with baseline. Complete suppression of inducible ventricular tachycardia at all levels of stimulation was obtained in 11/30 of these patients, and ventricular tachycardia cycle length was slowed by > 100 ms in one case. The response rate at each of these three electrophysiologically active doses was similar. Acceleration of induced ventricular tachycardia compared with baseline was found in just one

patient receiving 9.0 mcg/kg and there were no other adverse effects.

Intravenous dofetilide at doses of 3.0 to 9.0 mcg/kg prolonged ventricular refractoriness and achieved a response rate of 40% (12/30) with a low incidence of adverse effects. This favourable efficacy rate and excellent safety profile suggest that dofetilide should be further evaluated in the treatment of recurrent ventricular tachycardia.

Is QT interlead variability an arrhythmogenic marker?

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It has been suggested that increased QTc interlead variability (dispersion) on the surface electrocardiogram may be associated with high risk of serious ventricular arrhythmias. To determine whether QTc dispersion (calculated as maximum QTc—minimum QTc) can distinguish patients with from those without significant ventricular arrhythmias, we measured QTc interval in all leads of a surface electrocardiogram in 30 patients after myocardial infarction (aged 61 (7)) and 15 age matched normal control subjects. Fifteen myocardial infarction patients (group A) showed > 30 single ventricular extrasystoles/h, or ventricular tachycardia, or both, and the other 15 showed < 10 single ventricular extrasystoles/h and no ventricular tachycardia (group B). No myocardial infarction patients had evidence of conduction delays or were on antiarrhythmic medication. Myocardial infarction patients showed longer QTc (465 (21) v 418 (17) ms, $p < 0.01$) and greater QTc dispersion (75 (24) v 35 (9) ms, $p < 0.01$) compared with controls. Group A patients showed lower radionuclide ejection fraction (23 (4) v 36 (5)%, $p < 0.02$) and longer QTc (480 (17) v 440 (23) ms, $p < 0.05$) compared with group B; however, QTc dispersion was similar between groups A and B (79 (27) v 73 (20) ms respectively, NS).

Myocardial infarction patients show longer QTc and greater QTc dispersion compared with normal people; QTc dispersion alone, however, cannot distinguish myocardial infarction patients from those without serious ventricular arrhythmias.

Energy requirements of epicardial atrial defibrillation with bidirectional and monophasic waveforms

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Bidirectional waveforms are established in ventricular defibrillation, but their value in atrial defibrillation is unknown. We compared a monophasic and a bidirectional waveform in epicardial atrial defibrillation. The two waveforms were evaluated in 21 patients undergoing coronary artery bypass grafting. One hundred shocks were randomised, with up to six atrial shocks administered in each patient. The monophasic was an eight ms, truncated exponential waveform; the bidirectional was an eight ms, dual capacitor waveform with equal first and second phase duration and leading edge voltage. The first and second

phases were separated by 0.01 ms. Delivered energy was controlled by the stored voltage. Cardiopulmonary bypass was achieved without cardioplegia by alternating cross clamping and ventricular fibrillation at a systemic temperature of 31°C. Atrial fibrillation was induced on bypass after the first venous graft by the application of A/C current to the right atrial appendage. Atrial shocks were delivered through customised, contoured, stainless steel paddles applied to the posterior left atrial wall (surface area 11 cm²; cathode for the first phase) and to the anterior right atrial wall (surface area 26 cm²; anode for the first phase). All shocks were synchronised with the ventricular R wave. For the monophasic waveform the delivered energy (Joules) associated with 50% success (E50) was 1 (0.8) and with 80% (E80) success was 3 (2.4); for the bidirectional waveform the E50 was 0.3 (0.1) ($p = 0.08$) and the E80 was 0.4 (0.1) ($p < 0.05$).

Less energy is required in epicardial atrial defibrillation with a bidirectional than a monophasic waveform. This may have implications for both transthoracic atrial defibrillation and possible future development of an implantable dual chamber defibrillator.

A new philosophical approach to the electrocardiographic diagnosis of ventricular tachycardia

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Ventricular tachycardia is the prognostically important differential diagnosis of a broad complex tachycardia, but the current electrocardiographic rules tend to result in the overdiagnosis of supraventricular tachycardia. This is due to the number and complexity of the rules for the diagnosis of ventricular tachycardia, and in their absence, the diagnosis of exclusion of supraventricular tachycardia. This study sought to reverse this strategy using simple rules, widely applicable in electrocardiographic diagnosis, for the positive diagnosis of supraventricular tachycardia, with ventricular tachycardia the diagnosis of exclusion. Supraventricular tachycardia was the diagnosis if the electrocardiographic pattern was typical of that produced by bundle branch block. Typical left bundle branch block pattern has an rS or QS wave in lead V1, and an R wave in lead V6. Typical right bundle branch block has an rSR' pattern in lead V1 and an RS pattern in V6, the R greater than the S wave. Twelve lead electrocardiograms were collected from 102 patients with broad complex tachycardia (QRS width > 110 ms), 69 with ventricular tachycardia and 33 with supraventricular tachycardia, the diagnosis established by electrophysiology. A single blinded observer reported on all the electrocardiograms. The correct diagnosis of ventricular tachycardia was made in 63/69 patients and the correct diagnosis of supraventricular tachycardia was made in 24/33 patients (sensitivity for ventricular tachycardia 91%, specificity 73%). All six patients with ventricular tachycardia who were misdiagnosed as supraventricular tachycardia had a left bundle branch block pattern and five had right ventricular outflow tachycardia, the diagnosis suggested on the electrocardiogram by right axis deviation in the frontal plane.

These criteria, for the differential diagnosis of broad complex tachycardia, only require knowledge of classical bundle branch block patterns and were highly sensitive for the more important diagnosis, ventricular tachycardia.

Adenosine-sensitive atrial tachyarrhythmias: clinical and electrophysiological characteristics

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Several groups have suggested the use of intravenous adenosine in the diagnosis of both narrow and broad complex tachycardias. The termination of an arrhythmia by adenosine is thought to be strongly indicative of a junctional, rather than atrial, origin of the tachycardia. We report the clinical and electrophysiological findings in 12 patients with sustained atrial tachyarrhythmias that were slowed or terminated by intravenous adenosine (mean dose 0.13 mg/kg). All patients underwent full diagnostic electrophysiological study. Mean age of the patients was 39.5 and three had evidence of structural heart disease. Seven patients had normal electrocardiograms during sinus rhythm, one had left bundle branch block, and four had evidence of ventricular pre-excitation. Six patients had evidence of sinus node re-entrant tachycardia at electrophysiological study: adenosine terminated tachycardia in 5/6 patients and slowed the tachycardia without termination in 1/6 patients. Three patients had atrial flutter with ventricular pre-excitation: in all three patients flutter rate was transiently accelerated before termination occurred. Three patients had an incessant atrial tachycardia that could not be terminated by atrial extrastimuli ("automatic" atrial tachycardia): adenosine slowed and then transiently terminated this arrhythmia in all three patients.

At least three forms of atrial arrhythmia may be terminated by adenosine. These findings have implications for both the mechanism of atrial arrhythmias and for the use of adenosine in the diagnosis of arrhythmias. Adenosine is likely to have a useful diagnostic role in distinguishing sinus node re-entrant tachycardia from physiological sinus tachycardia.

Waist: hip circumference ratio (WHR) and its relation to cardiovascular risk factors in men and women

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Because of the lack of prospective studies of risk factors for coronary heart disease in British women and the reported increase in the risk of coronary heart disease with high waist:hip ratio, we assessed the relation of waist:hip ratio to fasting plasma insulin and lipoprotein concentrations in a stratified random sample of 1048 women (aged 25 to 69) and 824 men (aged 40 to 69) who attended a health survey in East Bristol. Compared with women with low waist:hip ratio, women with high waist:hip ratio (> 0.78) had higher concentrations of plasma insulin by 50% or 2.0 mU/l, total triglycerides by 45% or 0.47 mmol/l, total cholesterol by 10% or 0.5 mmol/l and total/high density lipoprotein cholesterol ratio by 13% or 1.0, but lower concentrations of total high density lipoprotein cholesterol by 11% or 0.16 mmol/l and high density lipoprotein subfraction 3 cholesterol by 13% or 0.12 mmol/l. Whereas men with high waist:hip ratio (> 0.95) had higher concentrations of plasma insulin by 80% or 4.0 mU/l, total triglycerides by

21% or 0.32 mmol/l, total cholesterol by 16% or 0.72 mmol/l, and total high density lipoprotein cholesterol ratio by 14% or 0.7 but lower concentrations of total high density lipoprotein cholesterol by 8% or 0.09 mmol/l and high density lipoprotein subfraction 2 cholesterol by 8% or 0.03 mmol/l. All these were statistically significant, and independent of age, body mass index, smoking habits, alcohol consumption (and taking oral contraceptives) in women but not in men, using multiple regression analysis.

High waist:hip ratio is associated with high levels of several cardiovascular risk factors and waist:hip ratio is an independent predictor of coronary heart disease in women.

Relation of diet to current smoking and time since quitting in the Scottish Heart Health Study

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Recent publications have suggested that cigarette smoking is associated with other potentially detrimental lifestyles, and that the diet of current smokers differs from that of non-smokers. In the Scottish Heart Health Study data on smoking, including time since stopping smoking, have been related to analysis of a food frequency questionnaire in 4265 men and 4770 women. Male current smokers had a higher consumption of energy, sugar, and alcohol than never smokers. After adjustment for energy intake they had a lower consumption of polyunsaturated fat, fibre, and antioxidant vitamins. Ex-smokers were intermediate and, when analysed by time since stopping, showed a progression from the dietary pattern of smokers towards that of never smokers. In women similar differences occurred between smokers and never smokers but the ex-smokers more closely resembled the never smokers and did not exhibit the clear trends seen in men. In both sexes ex-smokers had smoked as much as the current smokers in the past. This cross sectional study suggests that current cigarette smoking is associated with an altered diet which takes some years to change back after stopping smoking. Coronary risk in smokers is therefore compounded by an impoverished diet.

Cardiorespiratory symptoms before loss of employment

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Unemployed men are far more likely to report a variety of health problems than employed men. There are two possible explanations for this: (a) Loss of employment leads to higher levels of ill health and (b) men who lose employment have higher morbidity before their loss of employment. In the British Regional Heart Study 7735 men aged 40 to 59 randomly selected from one general practice in each of 24 towns in England, Wales, and Scotland were examined between 1978 and 1980. The data analysed are from the 6057 men who were employed for the previous five years. At the examination, men who subsequently experienced unemployment or early retirement (before 65) were significantly ($p < 0.05$) more likely to report experiencing various cardiovascular and respiratory symptoms than men

who remained continuously employed; 10.8% of continuously employed men reported chest pain on exertion or an episode of severe chest pain and 22.4% reported experiencing chronic bronchitis, breathlessness, or wheeze compared with 13.7% and 30.6% respectively of men who subsequently became non-employed. Objective measurements followed the same pattern; 6.2% of continuously employed men had electrocardiographic evidence of ischaemic heart disease and 9.0% had measured poor lung function, compared to 7.0% and 11.6% respectively of men who subsequently became non-employed. Reporting any of the cardiorespiratory symptoms significantly increased the risk of experiencing some non-employment in the next five years. Experiencing breathlessness or chronic bronchitis carried the greatest risk of non-employment (RR = 1.43 and RR = 1.31 respectively).

In determining whether loss of employment leads to higher levels of ill health, the health of the men before loss of employment must be taken into account.

What do we do with survivors of out of hospital ventricular fibrillation?

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The deployment of more defibrillators and paramedics on ambulances is leading to increasing numbers of patients surviving out of hospital ventricular fibrillation. We reviewed the in hospital course and management of 42 such patients (31 men: 11 women, mean age 64, range 44 to 87) admitted to four hospitals. Sixteen patients (group 1) developed myocardial infarction, seven had possible myocardial infarction (group 2), and there was no evidence of myocardial infarction in 19 patients (group 3). Patients in group 3 were significantly more likely than those in group 1 to have a past history of ischaemic heart disease (12/19 *v* 5/16) and to be taking diuretics (10/19 *v* 3/16) (both $p < 0.05$), and less likely to have experienced chest pain before cardiac arrest (5/19 *v* 15/16) ($p < 0.001$). Thrombolytic treatment was administered to eight patients in group 1 and three patients in group 3, with appreciable bleeding complications in three cases. Within the first 24 hours five patients in group 1 and seven in group 3 had further cardiac arrest. Similar proportions of patients in each group received lignocaine, but more patients in group 3 required other anti-arrhythmic drugs during this time (11/19 *v* 3/16) ($p < 0.05$). At discharge more patients in group 3 were receiving anti-arrhythmics other than β blockers (12/19 *v* 2/16). Of those in group 3, only eight underwent 24 hour Holter monitoring, four had exercise testing, five had echocardiographs, four underwent cardiac catheterisation, and two were referred for electrophysiological studies. Cardiologists were involved in the care of six of these patients, and saw five of the remainder in outpatient clinics.

The management of patients surviving prehospital ventricular fibrillation, particularly those at greatest risk of recurrent ventricular fibrillation, is inadequate, and is likely to remain so without increased cardiological input into their care and the development of management guidelines.